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(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

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METABOLIC CHANGES FOLLOWING THE INTRAVENOUS INJECTION OF POSTERIOR PITUITARY EXTRACTS AND THEIR CORRELATION WITH THE WELL-KNOWN PHARMACODYNAMIC ACTIONS OF THE DRUGS

E. M. K. GEILING AND A. M. DELAWDER

From the Department of Pharmacology, Johns Hopkins University

INTRODUCTION

The injection of pituitary extracts into man and animals causes significant changes in metabolism. During the last five years we have been engaged in studying various aspects of this action of the posterior pituitary secretion as administered in the form of the commercial post-pituitary liquid or pituitrin, and the separated fractions, prepared in 1927 by Kamm and associates (32), and now known as pitressin—the pressor, diuretic-antidiuretic, melanophore-expanding fraction—and pitocin, the oxytocic portion. Some of the results of our studies have appeared in the form of preliminary communications (19, 18), and the present paper gives more extensively the findings already reported, together with many additional data. The delay in presenting the work in more detail has been purposeful for the reason that we had hoped to perform our final experiments with pure preparations which have, unfortunately, not yet become available. Pitressin and pitocin are by no means chemical entities and neither fraction is free from the other, that is, pitocin contains some of the pressor fraction and *vice versa*. Undoubtedly, this accounts to some extent for certain inconsistencies in the degree of the responses elicited by different lots. In pharmacological work, especially with the endocrine principles, conservatism must be observed in drawing conclusions from experiments done with impure preparations, for at times the impurities may not only markedly modify the action of the hormone but may even have diametrically opposite physiological properties (17). However, in the absence of pure chemical individuals, we have made an intensive study of the post-pituitary preparations now available, in an effort to clarify some of the fundamental and hitherto less well recognized functions of the posterior lobe of the hypophysis.

E.M.K.

One of us (16) reviewed the experimental work dealing with the effect of pituitary extract on metabolism, and since then further work on the action of pituitary extracts and the separated fractions, pitressin and pitocin, has appeared. The results are by no means concordant. This is to be expected when it is remembered that the preparations were of varying potency and that the nature and the amount of the impurities and the preservative in some of the extracts may have caused a modification of the action. Furthermore, the experimental conditions, namely, the dosage, the route of administration, and particularly the times of observation varied widely in the different experiments. Hartmann (25) has recently emphasized the difference in the degree of the response obtained from hypophyseal extracts depending on the route of administration.

In 1924 Kolls and Geiling (33) reported determinations of the metabolism and cardiac output by the use of the Fick principle in trained, unanesthetized dogs injected intravenously with 1 cc. of Armour's pituitary liquid. They found a marked diminution in the oxygen consumption and a decrease in the cardiac output of their dogs. The observations were made about five minutes after injection, and no determinations were made in the later stages. Himwich and Haynes (26) reported a decrease in metabolism in normal male rats injected subcutaneously with large doses of pituitrin, and pitressin. Pitocin gave a slight, but definite, increased metabolism. Himwich, Finkelstein and Humphreys (29), using the Warburg technique, observed that under the influence of pituitrin and pitressin there is a depression of the oxygen consumption of excised tissue—testicle, diaphragm, and liver. Their results are, in our opinion, not convincing and will be dealt with more fully in the discussion.

In a preliminary communication before the Pharmacological Society at Montreal in the spring of 1931 Geiling, DeLawder and Rosenfeld (18) pointed out that during the height of the action of pitressin the venous blood becomes arterial in color and gaseous content. This, as we shall show later, is due to the fact that the tissues are not taking up the oxygen, while the drug, as gauged from the well-known changes produced in the skin capillaries and in the circulatory and respiratory systems, is exerting its main action (2) (33) (21)(22). Our attention was directed to this marked change in the color of the venous blood

during the course of our studies of the effect of the post-pituitary secretions on the blood sugar and phosphates. Our technique called for withdrawal of venous blood samples in quick succession after injection, and the bright red color stood out prominently in those samples taken at the height of the action.

In this connection mention must be made of some earlier observations by Draper and Hill (11), who found that there is an immediate fall in CO_2 combining power of the blood plasma after the intravenous administration of pituitary liquid, pitressin, and pitocin. We are not inclined to share the opinion of Draper and Hill that "the hormone in pituitary extracts which produces this acidosis and rise in blood sugar is, therefore, in all probability, chemically separate from both the pressor and oxytocic hormones." Whether or not their view is correct can not be put to a final test until such time as the various hormones now represented in the pitressin and pitocin fractions are obtained as chemical individuals.

That there results "a definite change in the pH of the blood towards the acid side following the intravenous administration of pituitary liquid (Armour) in doses of 1 cc. into unanesthetized dogs . . . . " was known to us prior to 1926 (16). It must, however, be frankly acknowledged that at that time this point was not pursued further, since the experiments were done with a view to aiding in the interpretation of the characteristic alterations in the respiration. A decrease in the pH of the blood was thought by us to be an added factor in the respiratory changes after pituitary injections, a subject which had engaged the attention of Loewi and Meyer (36), and Roberts (43) who ascribed the apneic periods following post-pituitary injections to constriction of the blood vessels in the medulla. Subsequent workers focussed attention on the changes in pH as being due to lactic acid accumulation, and our own work prompted the estimation of this constituent in the blood.

Several groups of investigators working independently have reported an increase in the lactic acid of the blood following the administration of post-pituitary preparations. Himwich and Fazikas (28) observed the effects on the lactic acid of the blood produced by the subcutaneous injection of 20–30 cc. of chloretone-free solution of each of the three posterior pituitary extracts (pituitrin 10 units per cc., pitressin 10 units

per cc., and pitocin 10 units per cc.) at half-hourly intervals into unanesthetized and amytalized dogs. The unanesthetized dogs receiving pitressin and one receiving pituitrin showed a consistent increase in the lactic acid of the blood drawn at two hour intervals, the maximum being reached at the second hour. In two experiments with pituitrin and in the cases with pitocin no significant changes were observed. These changes were not noted in amytalized dogs receiving any of the three extracts. Nitzescu and Munteanu (41) demonstrated an increased blood lactic acid reaching a maximum value twenty to thirty minutes after the intravenous injection of pituitrin (2–3 cc.) and pitressin (1.5–2.8 cc.) into unanesthetized dogs. In rabbits this peak was attained in about an hour after the subcutaneous injection of these drugs in approximately half the dosage. They studied the effect of pituitrin and pitressin on the lactic acid concentration of blood samples drawn simultaneously from the femoral artery and vein, and found an increase greater in the vein than in the artery. From this they conclude that the lactic acid produced after the administration of these drugs is formed in the muscle. The first samples of these latter experiments were drawn at thirty minutes after the injection, a fact which may explain the rather slight rise in the lactic acid. In our own experiments appreciable changes in lactic acid were obtained within five minutes after intravenous injection with doses as low as 0.3 cc. in unanesthetized dogs weighing 15 kilos.

Bischoff and Long (6), in a study of the effect of pitressin upon the carbohydrate reserves of normal rabbits, report an increase in lactic acid and blood sugar after "pharmaceutical and not physiological" doses. They comment on the fact that the hyperglycemia and lactic-acidemia do not run parallel.

A review of the experimental work dealing with the effects of post-pituitary extracts, pitressin and pitocin on the metabolism and cardiac output of human subjects will be discussed in another paper dealing with this phase of the work.

In *summary*, we have evidence from our own work and that of others that under the influence of pituitary liquid and pitressin there is a diminution in the oxygen consumption, an increase in the lactic acid, and immediately after injection of the drugs, a fall in the CO_2 combining power of the blood plasma.

However, it is to be especially noted that in contradistinction to the work of other observers our results were obtained under uniform conditions, and after a single intravenous dose within the usual pharmacological range. In addition we observed the effects of the drugs soon after injection, and traced them through the different stages of action including recovery. That this is the more desirable method of approach will be clear when it is remembered that the conditions existing at the height of the action of these particular drugs, which occurs immediately after intravenous injection, are almost opposite to those that are discernible during the recovery period, and if one repeats the injection or gives the drug by the continuous intravenous method, the effects may be merged. Furthermore, the factor of tolerance to the drug may become operative, since it is well known that repeated injections of posterior pituitary liquid are less effective than the initial dose. Undoubtedly, much of the disagreement in the results obtained by different investigators is more apparent than real, depending upon the time of observation, that is, the stage of action, as well as other factors such as dosage, route of administration, species of animal used and whether the conditions were basal or not. We are of the opinion that with posterior pituitary extracts, there is parallelism between physiological action and dosage only within a narrow range, for although 0.5 to 1.0 cc. can elicit the usual response in dogs, very much larger doses do not cause proportional reactions. In fact, excessive doses (10–30 cc.) of the drug are not lethal to dogs (28).

EXPERIMENTAL

Methods

Trained, normal, unanesthetized female dogs were used in our experiments. The animals were starved about twenty-four hours and were rested by lying on the table for about an hour, or longer, immediately preceding the experiment. Such trained dogs pay no attention to the injection of the drugs or to withdrawal of blood. In the experiments requiring exposure of the femoral vessels we secured the coöperation of Dr. Firor of the Department of Surgery, who quickly exposed the vessels with aseptic technique under local anesthesia without unduly exciting or disturbing the animal. We feel safe in saying that the

changes produced in our experiments are due to the drugs injected and not to any emotional or extraneous factors such as fear, pain, excitement, or blood stasis.

Analytical procedure

Blood carbon dioxide and oxygen were measured by the method of Van Slyke and Neill (46, 47) in an apparatus of the portable manometric type. Blood was drawn under oil in paraffin-sealed syringes, containing a minute quantity of dried sodium oxalate, stored over mercury in specially constructed containers, and "fixed" in the refrigerator between analyses, care being taken to allow adjustment to room temperature before each determination.

Lactic acid determinations were made according to the method of Friedemann and Kendall (14) in the West improved apparatus (49); blood sugars by the micro-method of Hagedorn-Jensen (23), the curves being checked in several instances by the Somogyi modification of the Shaffer-Hartman procedure (44); inorganic phosphate according to Fiske and Subbarow (13); hemoglobin readings according to Cohen and Smith (9).

Blood gases

The bright red color of the venous blood drawn 3–5 minutes after the intravenous injection of pitressin first led us to investigate its gaseous content. We found an early and pronounced rise from a normal value of 14–16 volumes per cent to 18–20 volumes per cent of oxygen in the blood taken from the superficial leg veins. Analyses of blood drawn simultaneously from the femoral artery and vein and, about a minute later, from the saphenous vein, indicate a practically identical oxygen content. The few experiments of this type which were carried out were necessarily limited to a brief period, because of the obvious impracticability of drawing so much blood from the subject without affecting the concentration. Accordingly, the results in Table 1 indicate the relations in arterial and venous blood gases merely at a point during the primary period of action and at the beginning of the second or recovery period—the stages which were of particular interest to us. It will be noted that, in the two experiments recorded, the oxygen and carbon dioxide contents become practically equal (due

allowance being made for experimental error) in the blood of both femoral artery and vein about five minutes after intravenous injection. At 20–25 minutes later when the venous blood becomes very dark, in marked contrast to the arterial and the previous bright red venous sample, there is an arterio-venous oxygen difference much more pronounced than normally.

Consideration of Table 2[1] demonstrating the effect of pitressin on the blood gases of the leg veins reveals that the oxygen concentration

TABLE 1

Effect of intravenous injection of pitressin on carbon dioxide and oxygen content of femoral artery and vein exposed under novocaine anesthesia

Dog. Weight = 14 kgm.

EXPERIMENT A					EXPERIMENT B				
Time	Femoral artery		Femoral vein		Time	Femoral artery		Femoral vein	
	CO_2	O_2	CO_2	O_2		CO_2	O_2	CO_2	O_2
	vols. per cent	*vols. per cent*	*vols. per cent*	*vols. per cent*		*vols. per cent*	*vols. per cent*	*vols. per cent*	*vols. per cent*
11:45	35.40	17.04	37.53	13.28	10:10	38.81	21.14	41.76	15.96
12:10	Injected 0.6 cc. pitressin into saphenous vein				10:27	Injected 0.6 cc. pitressin into saphenous vein			
12:15	29.34	17.85	28.93	18.22	10.32	39.16	20.19	39.34	19.27
12:33	29.17	16.28	36.24	5.42	10:52	35.79	19.31	43.68	7.03

* The difference in the initial arterial oxygen content in Experiment A (April 1) and Experiment B (April 14) may be explained by the fact that the dog had been acquired not long prior to the first experiment and was not so well nourished as after several weeks in the laboratory.

reaches a peak of 18–20 volumes per cent 4–8 minutes after injection, and thereafter undergoes a sharp drop to a value of 8–11 volumes per cent at 20–25 minutes. By drawing sufficient samples one can trace the course of the color changes in the venous blood of the limbs as it turns to a vivid arterial red shortly after injection, passes back through the normal stage to an unusually dark venous shade, which persists

[1] The experimental data presented are chosen largely to illustrate the points under discussion, and do not represent all of our experiments, which have been quite numerous in the long period of time we have been following the changes in one or other constituent of the blood.

during the period of abnormally low oxygen content, and then finally returns to the shade characteristic of normal venous blood about one and a half hours after injection at about the time the oxygen reaches the base line.

Simultaneously with the initial rise in oxygen content the carbon dioxide concentration of the venous blood drops suddenly to about 75–80 per cent of its resting value, the lowest level corresponding to the highest point in the oxygen curve. This may be explained by the dis-

TABLE 2

Effect of intravenous injection of pitressin on carbon dioxide and oxygen content of blood of superficial leg vein of dogs

WEIGHT OF DOG	DOSE	BLOOD GASES	NORMAL	TIME AFTER INJECTION					
				4 minutes	15 minutes	25 minutes	45 minutes	60 minutes	80 minutes
kgm.	cc.	vols. per cent							
14	0.5	CO_2	41.70	29.54	32.37	38.50	38.60	40.21	40.89
		O_2	16.36	21.65	19.03	11.15	13.75	17.09	16.55
				6 minutes			40 minutes		75 minutes
15	0.5	CO_2	43.72	32.11	34.93		41.41	44.40	44.07
		O_2	15.15	18.40	12.20		10.90	12.35	13.73
				3 minutes	20 minutes	35 minutes	45 minutes		
14	0.25	CO_2	44.84	39.62	38.48	41.74	42.51	Not followed	
		O_2	14.81	17.95	13.88	11.33	12.43		

placement of blood bicarbonate by the lactic acid formed during this stage and the elimination of the liberated CO_2 through the hyperventilation which may be a direct effect on the respiratory center or secondary to the blood changes affecting this center. Although the carbon dioxide returns quickly to a slightly subnormal value, the absolute return to the base line lags. This carbon dioxide retention no doubt aids in restoring blood bicarbonate during the period of payment of the oxygen debt incurred in the stage of anaërobic metabolism.

The effect of pituitrin merits special consideration. Although the effects on blood gases, lactic acid, etc. correspond well with those produced by pitressin, the whole reaction is more prolonged. Chart 1 shows the effect of 0.5 cc. pituitrin (S) on blood taken from the leg. The primary rise in oxygen concomitant with reddening of the blood persists longer, and the line between the maximum and minimum oxygen content (*i.e.*, inversely, minimum and maximum utilization by the tissues) slopes gradually, in contrast to the acute drop characteristic of

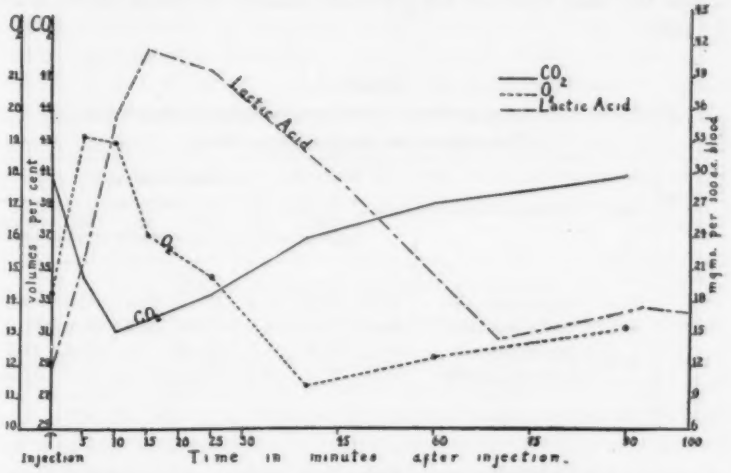

CHART 1. CHANGES IN CARBON DIOXIDE, OXYGEN, AND LACTIC ACID OF BLOOD DRAWN FROM SAPHENOUS VEIN OF DOG (21.7 KGM.) FOLLOWING INTRAVENOUS INJECTION OF 0.5 CC. PITUITRIN (*S*)

the termination of pitressin action and the commencement of the recovery stage. This prolongation of action may perhaps be ascribed to a greater admixture of inert proteins in pituitrin. Furthermore, in pituitrin, the separated fractions, namely, pitocin and pitressin, may be held in the form of a mother substance from which the pitressin may be more slowly liberated. This subject is fully treated in a recent paper by Abel (1) dealing with the question of the unitary versus the multiple hormone theory of posterior pituitary principles.

Lactic acid

During the period of oxygen deprivation in the tissues there is a rapid formation of lactic acid which quickly diffuses into the blood. The lactic acid concentration is appreciably increased at 5–8 minutes after the intravenous injection of pitressin and it continues to accumulate until it reaches a maximum concentration of about 3½ times the normal value 20–25 minutes after administration of the drug. The gradual return to the base line is complete in 1½–2 hours, *i.e.*, at about the same time the oxygen value reaches its pre-injection level (Table 3).

TABLE 3

Blood lactic acid changes produced by intravenous injection of pitressin into dogs

(Values given in mgm. per 100 cc. blood)

WEIGHT OF DOG	DOSE	SOURCE OF SAMPLE	NORMAL	TIME AFTER INJECTION					
				7–8 minutes	20 minutes	40 minutes	60 minutes	90 minutes	100–120 minutes
kgm.	cc.								
15	0.3	Saphenous vein	6.8	8.5	22.8	17	10.6	6.6	6.1
14	0.3	Saphenous vein	10.8	30.8	36.4	37.4	24.4	16.9	11.9
20.5	0.6	Saphenous vein	11.8	20.8	36.5	25.98		18.4	11.7
		External jugular	11.9	25.7	39.0	19.4		18.5	12.2
					27 minutes			80 minutes	
19	0.6	Saphenous vein	14.8	22.3	33.8			17.9	
		External jugular	11.7	21.2	38.9			14.0	

Such an increased formation of lactic acid with its consequent accumulation in tissues and blood is well known to occur under anaërobic conditions. Since diffusion of lactic acid into the blood stream is essentially secondary to its accumulation in the tissues, one can readily explain the fact that the peak in our lactic acid curves is usually noted when the period of high oxygen content of the venous blood has given place to a second phase of increased oxygen utilization by the tissues and, hence, low oxygen content of the venous blood. At least part of the oxygen utilized in this compensatory stage is needed in the re-synthesis of lactic acid to glycogen.

Whether muscle glycogen is depleted in the formation of the lactic acid under pitressin as is the case with epinephrine (10) must be demonstrated by further experimentation. Bischoff and Long (6) state, "even large doses of pitressin approaching the lethal dose have only a slight effect, if any, in lowering the muscle glycogen." The conditions of their experiments (continuous intravenous injection and subcutaneous injection of rabbits and sacrificing them 2–5 hours later) mitigate against any application of their data to our results. Nitzescu and Benetato (40) report a large decrease in the muscle glycogen of rabbits, whether in a starved or well nourished condition, after the daily subcutaneous injection of post-pituitary extract for four days (total dose 1 to 4 cc.). In our opinion determinations of muscle glycogen 10–15 minutes after a single, intravenous injection of pitressin, when lactic acid is being rapidly formed and before its re-synthesis to glycogen has begun, would give the most valuable and most readily measurable effect on the muscle glycogen stores. Such studies are now in progress.

Blood sugar and inorganic phosphates

The now well-known hyperglycemia following the injection of pituitrin, pitressin and pitocin was reported in 1927 by Geiling and Eddy (19). Their work has been corroborated by a number of investigators (31, 40, 4, 11, 27, 12). Lambie and Redhead (35) injected large doses of pituitrin into rabbits and found along with the hyperglycemia a transitory rise of inorganic blood phosphate. They also found that, in either human beings or in rabbits with hypoglycemia and low inorganic phosphate produced by insulin, pituitrin caused a rise in the phosphate. Similar results were obtained by us on dogs injected with insulin and later with pitressin (18). The findings of Nitzescu and Benetato (40) that pituitrin and pitressin cause, along with the hyperglycemia, a simultaneous rise in the inorganic phosphate of the blood, and that no such rise in phosphate is produced by pitocin although it causes a rise in blood sugar, were corroborated by us in the fall of 1930 (18).

In the light of the newer views regarding the phosphorus in the muscle components, such as phosphocreatine (phosphagen), adenosine triphosphoric acid, and hexose monophosphate (lactacidogen) (37, 38) it would seem indicated that further studies be made to learn more

TABLE 4*

Effect of the intravenous injection of pitressin and pitocin on sugar of blood drawn simultaneously from the femoral artery and vein (of dogs) exposed under novocaine anesthesia

(Values in mgm./100 cc. blood)

WEIGHT OF DOG	DOSE	SOURCE OF SAMPLE	NORMAL	TIME AFTER INJECTION								
				3–4 minutes	7–8 minutes	12 minutes	16 minutes	20 minutes	30 minutes	40 minutes	60 minutes	80–90 minutes
Pitressin												
kgm.	cc.											
21.5	0.6	Artery	100	102	138	133	127	116	112	102	102	96
		Vein	96	96	136	128	112	109	100	98	96	98
								25 minutes				
16.1	0.5	Artery	91	90	100	123		97		107	90	97
		Vein	90	93	102	107		91		83	88	91
					9 minutes							
16.3	0.7	Artery	107	125	162	148	136	128	114	111	112	111
		Vein	105	121	153	140	128	118	112	105	104	104
14.0	0.6	Artery	93	93	123	132		132	101		109	
		Vein	97	93	128	130		121	97		105	
Pitocin												
14.0	1.0	Artery	113	150	178	166	165	157	140	142	133	132
		Vein	113	145	142	155	155	151	139	132	128	130
				2 minutes				24 minutes		28 minutes		
15.0	1.0	Artery	116	135		178	150	134		128		
		Vein	114	130		152	150	128		128		
				6 minutes								95 minutes
16.0	1.0	Artery	96	160		172	156	158		145		124
		Vein	100	124		154	160	153		142		124

*The figures quoted in Table 4 were selected from a large mass of data, because they yield information upon the specific point concerning the state of the blood sugar immediately (3–5 minutes) after injection of the drugs.

about the origin and nature of the increased phosphate following pituitrin and pitressin injection.

The cause of the hyperglycemia produced by posterior pituitary extracts has not yet been determined satisfactorily or conclusively. The results of Achard, Ribot and Binet (3), and of Hines, Leese and Boyd (30) indicate a diminished utilization of sugar by the tissues under the influence of pituitrin. Our data (Table 4), though not conclusive, indicate that the rise of sugar in most cases is inappreciable within the first 3–4 minutes after intravenous injection of pitressin. The hyperglycemia during the period of maximum action of the drug is characterized by a small A-V difference, suggesting a lower utilization of glucose during this stage. The A-V difference becomes more pronounced during the period of increased oxygen uptake by the tissues. Under pitocin the sugar rises promptly and the A-V difference is large; these facts are suggestive of increased liberation of glucose (from the liver probably) and increased utilization in the tissues (7).

Effect on the external jugular blood

The effect of pituitrin and pitressin on the color and gaseous content of the blood of the external jugular vein is singularly different from that observed in the blood draining the limbs. Whereas the blood of the saphenous and femoral veins becomes arterial-like in character soon after the intravenous injection of these drugs, a sample collected from the external jugular vein almost simultaneously (within 1–2 minutes before or after the leg sample) is more venous-like both in appearance and oxygen content than the initial jugular blood. Chart 2 indicates the extreme divergence of the two oxygen curves immediately after injection, when the jugular oxygen falls as the saphenous or femoral oxygen rises. The jugular vein oxygen frequently continues its descent until its minimum value is attained 25–30 minutes after injection, returning to normal in about the same time as the femoral. Carbon dioxide concentration shows only a slight variation throughout. The lactic acid curves in the femoral and jugular veins follow each other fairly closely, rising with equal sharpness and reaching adjacent maximum values.

One should recall the fact that in the dog the external jugular

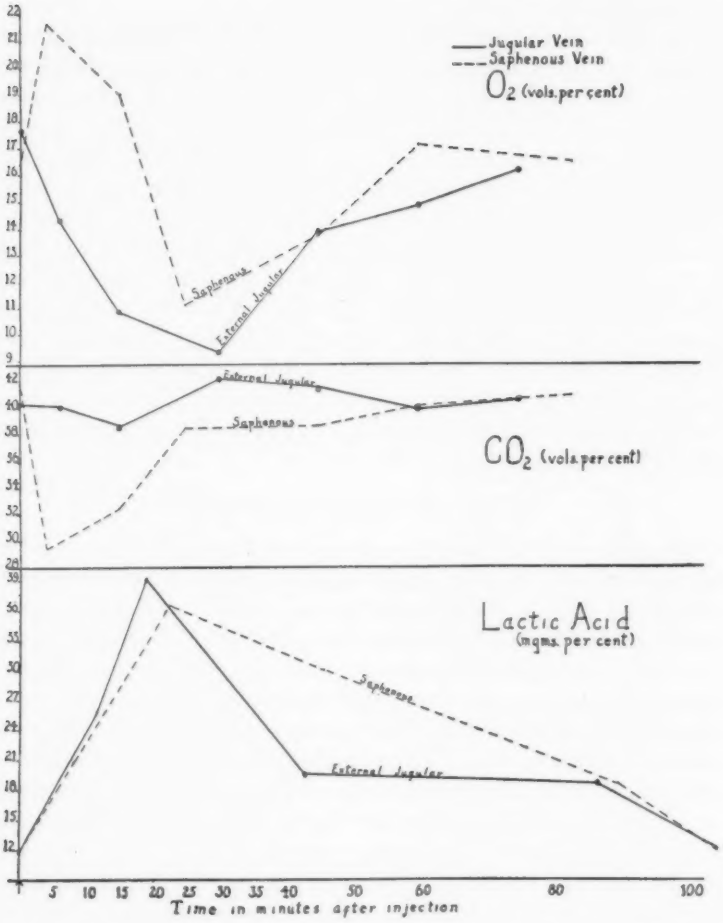

CHART 2. COMPARISON OF OXYGEN, CARBON DIOXIDE, AND LACTIC ACID CHANGES IN BLOOD OF SAPHENOUS AND EXTERNAL JUGULAR VEINS OF DOG FOLLOWING INTRAVENOUS INJECTION OF PITRESSIN (0.5–0.6 CC.)

veins drain not only the facial muscles, but also the brain and related tissues. It is in all probability a peculiar condition in the brain and its associated structures which is responsible for the blood changes in the jugular when contrasted with those occurring in the veins draining skin and muscle tissues exclusively. There are two possible explanations for the conditions in the jugular: either an increased brain metabolism or a decrease in the cerebral flow, or both. An augmented brain metabolism would account for the increased oxygen utilization, and a relatively high CO_2 output. In view of the recent experiments demonstrating that the intact brain can utilize lactic acid as well as glucose, one might expect a partial removal of the lactic acid from the arterial blood which under pituitrin or pitressin has an abnormally high content of this substance. An examination of our data, however, reveals about as high a concentration of lactic acid in the jugular as in the femoral or saphenous vein. It is further noteworthy that there is no apparent decrease in the carbon dioxide content of the jugular vein despite the presence of abnormal amounts of lactic acid, as in the femoral and saphenous veins.

Secondly, a decreased blood flow through the cerebral structures may account for the condition in the jugular blood. Wolff (50) reports that pituitary extracts intravenously injected into dogs produce a constriction of the pial arteries, arterioles, veins, venules and minute vessels. (See also Miwa, Ozaki and Shiroshita, 39). Loewi and Meyer (36) as well as Roberts (43) report a constriction of the vessels of the medulla under pituitrin. These facts would fit in well with the explanation suggested above. It is quite clear to us that the necessity for further investigation of the effect produced by pituitrin and pitressin either on the brain metabolism or the cerebral circulation as reflected in such a changed jugular blood is imperative. However, while the present experiments were directed more to the striking, though contrasting, effect produced by these drugs on the skeletal muscle, they also emphasize the fact that the response to a drug may vary markedly in different regions of the body.

Destruction of the physiological activity of pitressin by alkali

It is known that the pressor and oxytocic activities of post-pituitary extracts, as also pitressin and pitocin, are destroyed by treatment with

alkali. In 1928 Geiling and Eddy (19) demonstrated that the sugar-raising property of pitressin (then known as vasopressin) is practically

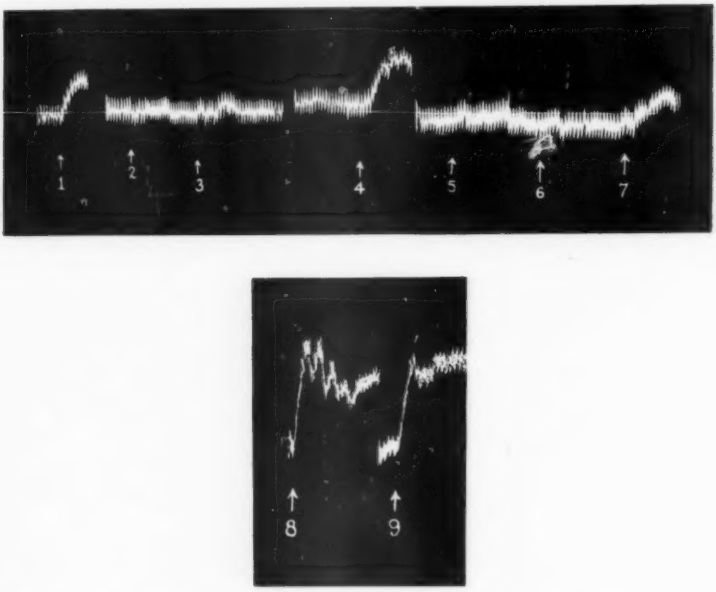

FIG. 1. CAT, WEIGHT, 2.6 KGM.; PHANODORN ANESTHESIA, 80 MGM. PER KGM. INTRAVENOUSLY

Tracings: No. 1, 0.1 cc. 0.1 mgm. Standard Powder; No. 2, 0.3 cc. injured pitressin; No. 3, 1 cc. injured pitressin; No. 4, 0.1 cc. of 1:10 dilution of pitressin (uninjured); No. 5, 0.1 cc. pitocin (CE) (0.1 pressor unit per cc.); No. 6, 0.2 cc. pitocin (CE) (0.1 pressor unit per cc.); No. 7, 0.1 cc. 0.1 mgm. Standard Powder; No. 8 (0.1 cc. = 0.1 mgm. Standard Powder); No. 9, 0.1 cc. commercial pitocin (No. 160).

This chart illustrates the loss of pressor activity by treating pitressin with alkali (tracings 2 and 3), and that the specially prepared pitocin (CE) possesses practically no pressor activity (tracing 5 and 6). Compare these with tracings 8 and 9 obtained on another cat injected with Standard Powder and commercial pitocin, respectively. Note the definite pressor response in the latter case.

completely destroyed by this treatment and that much of the hyperglycemic activity of pitocin (oxytocin) disappears under a similar pro-

cedure. In order to determine whether the other physiological properties are similarly destroyed, we treated pitressin with an equal volume of 2N NaOH twenty-four hours at room temperature, and neutralized before injection with 2N HCl. The blood pressure tracings show clearly that the pressor activity of pitressin is practically destroyed by the alkali (fig. 1).

This inactivated pitressin, when injected into one of our dogs, produced only a slight reddening of the blood, a negligible increase (about one volume per cent) in the O_2 content of the blood, no change in the concentration of CO_2 and an inappreciable rise in the lactic acid of the blood. This experiment, besides serving as a control, furnishes clear proof that the various physiological changes produced by pitressin, such as pressor and hyperglycemic actions and also the metabolic changes, studied in this paper, can all be annulled by treatment with alkali. It seems logical to us to infer that the above mentioned physiological actions manifested by the pitressin fraction are all due to a single compound. The possibility that there may be two or more chemically similar substances responsible for these actions is, however, not eliminated by the above experiment.

Pitocin

Due to the complicating presence of small amounts of pitressin in the usual commercial pitocin preparations, and the fact that the characteristic effect of the former on the blood constituents takes precedence in the period immediately following intravenous injection, our results on pitocin for a time exhibited the inconsistency noted by previous workers. However, we were fortunate to obtain from Dr. Oliver Kamm a specially prepared and purified sample of pitocin containing 10 oxytocic units and only 0.1 pressor unit per cc. The results obtained with this special preparation are in marked contrast to the changes brought about by pitressin. There is a diminished oxygen content of the venous blood, with no marked change in the CO_2 or lactic acid content.

Although a more complete study of the metabolic changes induced by pitocin will be presented in a separate communication, the accompanying figures (Table 5) are included to indicate that the inconsistent results secured with pitocin are due to its contamination by pitressin.

TABLE 5

Comparison of gaseous and lactic acid changes in the blood of the leg vein following intravenous injection of commercial pitocin containing 5 per cent pressor substance (lot No. 160) and a highly purified oxytocin (CE)

See blood pressure tracings for comparative amounts of pressor substance contained therein.

SOLUTION INJECTED	WEIGHT OF DOG	GASES	NORMAL	TIME AFTER INJECTION						
				4 minutes	10 minutes	15 minutes	25 minutes	50 minutes	75 minutes	90 minutes
Carbon dioxide—oxygen										
	kgm.	*vols. per cent*								
Commercial pitocin, lot No. 160, dose = 1.0 cc.	14	CO_2	42.14	36.64	40.51	41.07	41.22	42.44	43.11	
		O_2	14.03	16.65	11.56	9.43	10.64	11.19	11.20	
				8 minutes	12 minutes	20 minutes	40 minutes			
	15	CO_2	40.98	33.64	33.40	35.08	39.45			
		O_2	15.52	15.31	16.14	15.29	14.53			
				3 minutes	8 minutes	16 minutes	25 minutes	45 minutes	60 minutes	
Purified oxytocin (CE), dose = 1.0 cc.	20.65	CO_2	37.49	39.32	38.77	38.54	38.93	40.10	39.91	41.43
		O_2	17.17	12.84	13.22	13.95	14.31	14.86	15.32	14.00
				4–5 minutes	9–10 minutes	16–18 minutes	30 minutes	50 minutes	70 minutes	
	20.5	CO_2	41.40	42.20	42.21	42.73	43.15	43.30	43.22	
		O_2	13.25	8.79	9.04	9.87	11.01	9.60	11.07	
Lactic acid (mgm. per 100 cc. blood)										
				3 minutes	8 minutes	15 minutes		45 minutes	60 minutes	120 minutes
Commercial pitocin, lot No. 160, dose = 1.0 cc.	13		7.4	11.4	13.8	18.1	18.3	14.8	14.1	8.9
				4 minutes		12 minutes	25 minutes	50 minutes	90 minutes	
Purified oxytocin (CE), dose = 1.0 cc.	14.4		8.1	9.3	8.6	9.2	10.9	9.9	8.8	

Pitocin No. 160, one of the usual commercial preparations, which contains an effective quantity of the pressor substance as shown by the accompanying blood pressure tracings (fig. 1), gives a definite, though somewhat slight and transient pitressin-like effect when injected intravenously into the unanesthetized dog. On the contrary, the purified preparation (CE), producing no pressor response, causes in the unanesthetized animal a more or less pronounced darkening of the venous blood 5–10 minutes after intravenous injection.

Comparison with cyanide action

One may call attention to the parallelism between some of the physiological effects of cyanide, and those of pituitrin and pitressin. Claude Bernard (5), in 1857, recorded the fact that under the influence of cyanide the venous blood becomes bright red. Geppert (20) later studied the cause of this change and found that the bright color of the venous blood was due to a diminished utilization of oxygen by the tissues. He concluded that under cyanide the tissues lose the capacity to take up oxygen—a condition of internal asphyxia. Gaethgens (15), before Geppert (20), used cruder methods for gas analysis and did not obtain concordant results. Zillessen (51) found that under heavy intoxication with cyanide in dogs the lactic acid and the sugar in the blood are increased.

Under cyanide then we have a bright red venous blood, high O_2 content and increased lactic acid and sugar—a condition of internal asphyxia or anaërobic metabolism which is also produced by pituitary liquid (pituitrin) and pitressin. These drugs, however, differ markedly in toxicity and duration of action.

Warburg (48) ascribes the action of cyanide to its combination with the iron in the cell respiration ferment, thereby preventing its normal catalytic function.

DISCUSSION

The mechanism by which pituitrin and pitressin bring about the aforementioned effects must be left open at present. For purposes of discussion the changes in blood chemistry resulting from the administration of pituitrin and pitressin may be divided into two phases: a brief period of anaërobic tissue metabolism followed by a more prolonged stage of aërobic recovery.

We may briefly review the known physiological changes induced in the unanesthetized dog by these drugs. There are definite disturbances in the circulatory and respiratory systems. During the period when the venous blood becomes arterial in character, *i.e.*, that stage resembling anaërobic metabolism in the tissues, the heart rate is slowed, decreasing from about 70 to below 40 beats per minute, the cardiac output is reduced, the blood pressure for the greater part of the time is elevated, the skin capillaries are constricted, the veins are distended, and the respiratory rate is very rapid. The blood draining the limbs during this stage shows a high oxygen value, a rapidly rising lactic acid concentration, and a lowered carbon dioxide content; the blood sugar and inorganic phosphate are also increased. This may be regarded as the stage of maximum activity of pitressin and pituitrin.

In the recovery period immediately ensuing and lasting for a considerable time the picture is reversed: increased oxygen consumption by the tissues, lowering of lactic acid (more fully explained in the text) and increased retention of carbon dioxide. This period resembles in duration and blood picture the recovery period following brief severe muscular exercise. The changes in the blood and tissues can be brought about with small intravenous doses (0.1 cc. to 0.2 cc. of pitressin or surgical pituitrin) and in such cases the panting is slight or absent, although the respiratory rate may be increased.

Among the possible causes which may account for the failure of the exchange of oxygen between blood and tissues are:

1. A markedly accelerated rate of blood flow through the tissues.
2. A change in the condition of the capillaries.
3. An inability of the tissue cells to take up oxygen.
4. A temporary inability of the blood to give up its oxygen. (This last named condition is very improbable and could be excluded by a study of the oxygen dissociation curve of pituitrinized blood.)

The causative mechanism may thus be viewed as operating either through the vascular system or through a direct action of the drugs on the tissue cells. Under vascular changes we must consider blood pressure. According to Gruber (21), in unanesthetized dogs the arterial tension following the intravenous injection of pitressin (0.5 cc.) undergoes various changes: a primary rise within the first minute,

a fall within the second minute and a subsequent prolonged rise. This factor would tend to increase the rate of blood flow through the tissues. During this early period, however, the skin capillaries are markedly contracted, causing the visible mucous membranes and skin to appear blanched. The cardiac rate for the most part is diminished and the heart output is reduced. These latter facts speak against a general increase in blood flow but would not necessarily indicate a diminished rate of flow through all the capillaries.

Krogh (34) states that pituitrin "appears to have no effect in minute doses on the rate of inflow of blood, but a distinct effect on the blood color, brought about by constriction of skin capillaries and venules." He refers to pituitrin as containing a capillary hormone which has thus far been shown only to constrict the cutaneous capillaries. He concedes the possibility of the drug reacting differently or not at all on other organs. Later Hartman, Evans and Walker (24), using anesthetized or decerebrate cats, studied the capillaries in the skeletal muscles and report that under pituitrin the smallest vessels are dilated and the largest ones are constricted. Clark (8), who also used anesthetized or decerebrate cats, with both vagi sectioned, found that pitressin, intravenously administered, causes a redistribution of the blood in the body so that the intestine contains much less and the muscles more; the skin and connective tissues usually have less, but if the blood pressure is greatly increased, may contain more. He concludes from plethysmographic records of the volume of voluntary muscle (using the stump remaining after the amputation of the foot and removal of the skin) that pitressin produces a slight increase in volume due to a passive dilatation which results from the rise in blood pressure. However, if the blood pressure rise is prevented by means of a Bayliss mercury compensator, the drug has a feeble constrictor action. Ssentjurin (45) perfused the vessels of the isolated ear of a rabbit with varying concentrations of pituitrin and noted a constriction of the arterioles and perhaps capillaries. Repeated perfusions with the drug give lessened responses, until finally a dilatation of the vessels may occur. The studies of Hartman and coworkers and of Clark were carried out in cats under anesthesia or decerebrated. Whether these results will apply in the case of unanesthetized dogs is open to question, particularly since in dogs the effects of pitressin on

the blood pressure differ in unanesthetized and anesthetized animals. With anesthesia the rise in arterial pressure is much more pronounced than without. The available facts in the literature do not appear to offer much light on the state of the muscle capillaries in the unanesthetized dog under the influence of pituitrin or pitressin within the dosage range of our experiments. One could conceive of the apparent anaërobic metabolism observed by us in the early period of pituitrin and pitressin action as being due, in part if not wholly, to anoxemia of the tissues induced by capillary constriction. To account for the arterial-like character of the venous blood one would have to assume a simultaneous shunting of the arterial blood to the venous side through patent larger channels. Should the muscles have arterio-venous connections such as those observed by Heimberger in human skin, the blood passing through such avenues would, according to Krogh (34, 25a) "probably fail to give off the normal amount of oxygen and substances which it is supposed to carry to the tissues, because it is not exposed to the thin walls and large surface of the capillaries." During this period of tissue asphyxia there would be an accumulation of lactic acid which in turn at a certain concentration might cause the capillaries to dilate and thus set into action the period of increased oxygen utilization, or recovery period. If this is true, our observations would be explainable on the basis of a mechanical interference in the normal exchange of metabolites between tissues and blood.

One can not readily rule out a changed permeability of the capillary wall, since this itself may be altered by the constrictor effect of the drugs.

Making due allowance for the possible influence of the above named vascular factors, one must consider a direct effect of the drug upon the tissue cells in such a manner as to render them temporarily unable to take up the oxygen. This would suggest a cyanide-like action of the post-pituitary secretion. The excised tissue respiration experiments with the posterior pituitary extracts in the Warburg apparatus as carried out by Himwich, Finkelstein and Humphreys (29), would afford proof of a diminished oxygen consumption due to a direct effect upon the tissue cells, were it not for the fact that their results are unconvincing. Our criticisms are based on a preliminary communication

only in which it seems to us their data lack adequate controls (*e.g.*, with other tissue extracts and with the inactivated products, since the results with impure pitocin vary in the same direction, if at all). The doses used by them were entirely out of proportion to the amount generally employed in the intact animal. In several instances the drugs constituted over 8 per cent of the medium in which the tissues were suspended. We offer these obvious criticisms rather reluctantly for we believe that experiments of this type, carried out with appropriate concentrations of the drugs and with proper controls, would be most helpful in pointing to the site of action of the post-pituitary hormone and would afford a satisfactory explanation of the findings in the intact subject.

The secretion of the posterior lobe of the pituitary gland is the more unique in that it contains at least two components which in most respects have opposite physiological actions, and thus may act in unison to yield a balanced mechanism.

It is clear from the work reviewed and from our own data that the extracts of the posterior pituitary gland, when injected into the body, can act rapidly and efficiently in regulating the exchange of metabolites between blood and tissues. Previous workers have failed to correlate these changes with the well-known pharmacodynamic effects produced by the injection of these drugs. Assuming that the extracts used represent the hormone as it functions in the body, then after the injection of even small doses of the extracts there would result a concentration of the hormone in the blood far greater than under normal conditions. Whether the physiological changes induced by such concentrations can be regarded as an exaggerated hormonal effect, or would be produced by any substance acting through one or both of the mechanisms previously discussed (the capillary constrictor effect or a direct action on the tissue cells) remains uncertain. Until these points are settled one can do no more than propose the following hypothesis: *If we postulate that the action of the extracts represents that of the posterior pituitary hormone as it exists in the body, and that the injection of such extracts, although it be a crude imitation under exaggerated conditions, simulates the normal action of the hormone, then the posterior lobe of the hypophysis functions in the body as one of the regulators of metabolism.*

SUMMARY

Our experimental results were obtained under essentially uniform conditions, with relatively small doses of the drugs given in single intravenous injections to resting, normal, unanesthetized dogs. The responses were examined at frequent intervals until the period of recovery was completed, thus enabling us to establish an intelligible correlation between the changes in the various blood constituents and the concurrent pharmacodynamic reactions during the successive stages.

From our data the following conclusions seem warranted: After the injection of pituitrin and pitressin there follows for a short period—the stage of maximum action—a state resembling anaërobic metabolism in the tissues drained by the superficial and deep leg veins of dogs. During this time the venous blood is characterized by an arterial-like color and oxygen content, a lowered carbon dioxide tension, a rapidly rising lactic acid concentration, increased glucose and inorganic phosphate. This is the period of decreased cardiac output and lowered basal metabolism. Following this stage of tissue asphyxia is the recovery period when conditions are reversed: an abnormally dark venous blood, increased utilization of oxygen and production of carbon dioxide by the tissues, and a continued rise and subsequent gradual return of blood lactic acid to the pre-injection level.

Blood drawn from the external jugular vein (having a mixed drainage area, brain, muscle, etc.) in the period of the so-called"maximum action" of pituitrin and pitressin indicates a different effect of these drugs in this region. In contrast to the arterial-like leg sample, the jugular blood is more venous in color and has a decreased oxygen content, only a slight, if any alteration in the carbon dioxide concentration, and a lactic acid increase similar to that in the femoral blood. The return of the basal level roughly parallels the recovery period indicated in the blood draining the limbs.

Pitressin inactivated with respect to the pressor response by treatment with alkali simultaneously loses the other above-mentioned physiological properties.

The usual commercial pitocin products, containing definite amounts of the pressor substance, give a transient pitressin effect. Purified

pitocin extracts, containing negligible amounts of the pressor principle, produce an effect differing, in a mild degree, from that of pituitrin and pitressin, namely, an increased tissue metabolism indicated by a slightly darker venous blood, with an oxygen content lower than normal.

The mechanism by which the changes described are effected is as yet unknown; it may be either vascular or cellular or both.

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DIABETES MELLITUS AND MYXEDEMA

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The co-existence of diabetes mellitus and hyperthyroidism is infrequent enough to cause comment, but the concomitance of diabetes mellitus and hypothyroidism, or rather myxedema, is sufficiently unusual to merit reporting. Two cases gleaned from the records of the Johns Hopkins Hospital, one with post-mortem investigation, form the basis of this communication.

The incidence of diabetes mellitus associated with hyperthyroidism has been shown by Joslin and Lahey (1) to be 1.34 per cent. They reviewed the case histories of 4917 true diabetics and 3869 cases of hyperthyroidism that came to operation and found only 75 instances in which the two diseases were present. In contrast to this comparative frequency Joslin mentions that one case of myxedema was found co-existing with diabetes mellitus, an incidence of 0.02 per cent.

Holst (2) in 1923, reported a case of thyrotoxicosis in a woman of 36 years, who had symptoms dating back five years. Subtotal thyroidectomy was performed in July 1918. When seen again in February 1919, sugar in the urine was a repeated finding. The patient was still nervous, but had gained 6.5 kg. in weight. In June, 1921, she was found to be much improved as far as thyroid symptoms were concerned, but now displayed the clinical evidences of myxedema. There was no glycosuria and 100 grams of glucose by mouth failed to provoke an excretion of glucose in the urine.

Brown (3) in 1924 observed a 55-year-old female who, with a low basal metabolism, maintained a fasting sugar level in the blood of 137 mgm. per cent and who, when the metabolism was raised by the use of thyroid extract by mouth, showed a progression in the severity of the diabetes, the fasting blood-sugar rising to 433 mgm. per cent.

In 1926, Wilder (4) observed a very interesting child, who developed signs of diabetes at the age of fifteen months. The malady was con-

trolled by dietary means until the age of three years when there developed definite evidence of cretinism with a basal metabolism estimation of −45 per cent. The fasting blood-sugar was 120 mgm. per cent. On substitution therapy with thyroid extract the rate was elevated to −10 per cent, the blood-sugar rose to 145 mgm. per cent, and the child developed all of the signs of diabetes mellitus with acidosis. Removal of the substitution therapy resulted in a return to the previous status of mild diabetes and severe juvenile myxedema.

Wright (5) saw two cases within two days' time in 1926 in young women of twenty-four and eighteen years of age. Both had been considered subjects of severe diabetes for about two years. The basal metabolism determinations were at the levels of −26 and −28 per cent, respectively. Both were given thyroid extract, dietary supervision and insulin, and although they lost weight and felt better, there was no decided change that might have been predicted from the change in the metabolic level. Wright stressed the fact that the diagnosis was made not solely on account of the low basal rates, for in addition both manifested decided skin changes, dryness and coarseness of the hair, lethargy, and the usual signs associated with myxedema.

Jamieson (6) reports the case of an interesting 37-year-old male who had been ill with diabetes for thirteen years. He developed during the course of a year alopecia, dryness and coarseness of the skin and a major psychosis. The metabolism level was −36 per cent, the fasting blood-sugar 120 mgm. per cent. A glucose tolerance curve showed a rapid rise of the blood sugar to a high level and a delayed return to normal. He was treated with extract of the thyroid gland and with insulin. The results were equivocal but were best when small doses of both thyroid extract and insulin were employed.

Joslin (7), in the 1928 edition of his text mentions three cases. Protocol 2899 gives an account of a 53-year-old woman who had a basal metabolism of −32 per cent, a fasting blood-sugar of 100 mgm. per cent and no glycosuria. Nine months later she had developed polyuria, pruritus vaginalis, amblyopia, and there was 8.4 per cent of glucose in the urine. Her status six years later revealed a maintenance intake of thyroid extract of five grains, a metabolism level of −9 per cent with a fasting blood-sugar of 310 mgm. per cent.

Case 3565 was that of a 35-year-old woman who developed diabetes.

Eight years later three was a blood-sugar of 328 mgm. per cent. Eleven years later there was 0.7 per cent glucose in the urine and a metabolism of −20 per cent. "On thyroid extract promptly improved."

Case 5143. This patient had a low basal metabolism in 1913 and was given thyroid extract at another clinic. When seen by Joslin the basal metabolism was −17 per cent, but there was no other evidence of myxedema. In 1918 at the age of thirty-eight, the diabetes was controlled with 30 units of insulin, while the patient was on a diet containing 130 grams of carbohydrate.

The most recently recorded coincidence of the two ailments is the case reported by Carey (8). He records a white male of 44 years seen in 1921. The patient presented the typical features of myxedema with a basal metabolism of −36 per cent. After three months' treatment with six grains of thyroid extract every day, the patient showed great subjective improvement and the metabolism had reached +2 per cent. There was no urinary sugar. Seven years later in 1928 the patient developed the characteristic symptoms of diabetes mellitus. In 1929 he was found to have a basal metabolism of −17 per cent. He had been taking thyroid extract, however, every day to avoid lethargy. The blood sugar was 174 mgm. per cent, and he was excreting 10 grams of glucose in the urine every day. As the extract was administered in larger doses the metabolism rose to +1 up to +12 per cent, the blood sugar reaching the level of 285, and 30 units of insulin were needed to combat the acidosis.

Here too the diabetes was activated as the metabolism was raised. Interestingly enough the maintenance dose of thyroid extract had fallen from 5 to 2 grains a day.

An investigation of the records of patients admitted to the medical wards of the Johns Hopkins Hospital from January 1, 1920 to May 31, 1931 reveals a total of 37,190 medical admissions. This number included 1,243 cases of diabetes, an occurrence rate of 3.3 per cent. There were 919 new cases seen in the diabetic dispensary of the Johns Hopkins Hospital from 1927 to 1931 inclusive. A rough compilation indicates that approximately 3000 cases of diabetes have been treated in this institution in the 1920–1931 interval. During the same period there were 22 patients with typical myxedema. Myxedema and dia-

betes mellitus co-existed in only two individuals. The protocols follow (Chart I).

Case I. T. G. Unit 9973. A 57-year-old white, unmarried laborer was first seen on May 8, 1925. At that time he complained of numbness of the hands and feet, increased thirst, polyuria, weakness and loss of weight. These symptoms had been present for the past two years.

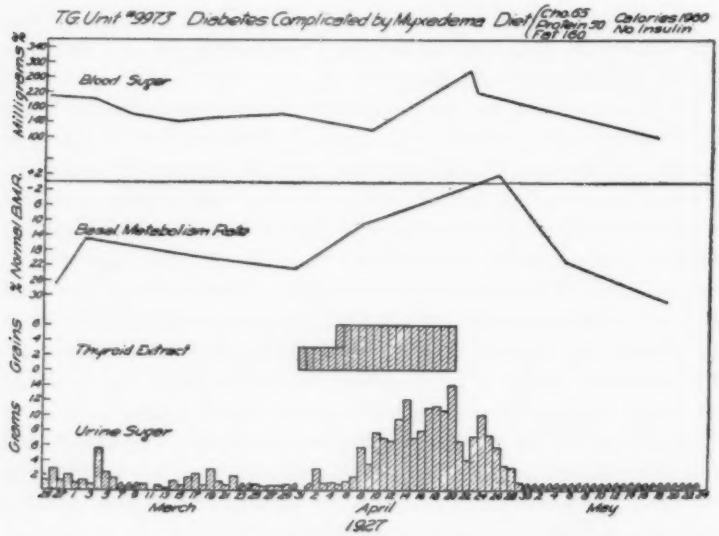

CHART I. *Case I.* Showing the effect of thyroid extract on the basal metabolism, the blood sugar and the glycosuria; the rise of the sugar, the appearance of large amounts of sugar in the urine, and the increase in metabolic rate which occur during the administration of thyroid extract. Regression of signs with discontinuance of therapy.

His father had died at the age of 65 of "neuralgia of the heart" and his mother had died suddenly at the age of 55. One brother who had heart disease had died at the age of 45. There was no family history of diabetes, goitre, or cancer.

The patient had always been in robust health. On account of a severe pyorrhea all the teeth had been removed a year before admission. There were no symptoms referable to the circulatory or respiratory systems. He had lost thirty pounds during the last two years.

On admission he was found to be markedly undernourished, but well developed

and in no pain. The height was 168 cm., the weight 41.3 kilograms. The calculated weight for a male of his age was 70 kilograms. The pulse rate was 80, the temperature 98.4°F. by rectum. The skin was rather thin, moderately warm and moist. The hair was of normal texture and distribution. There was no

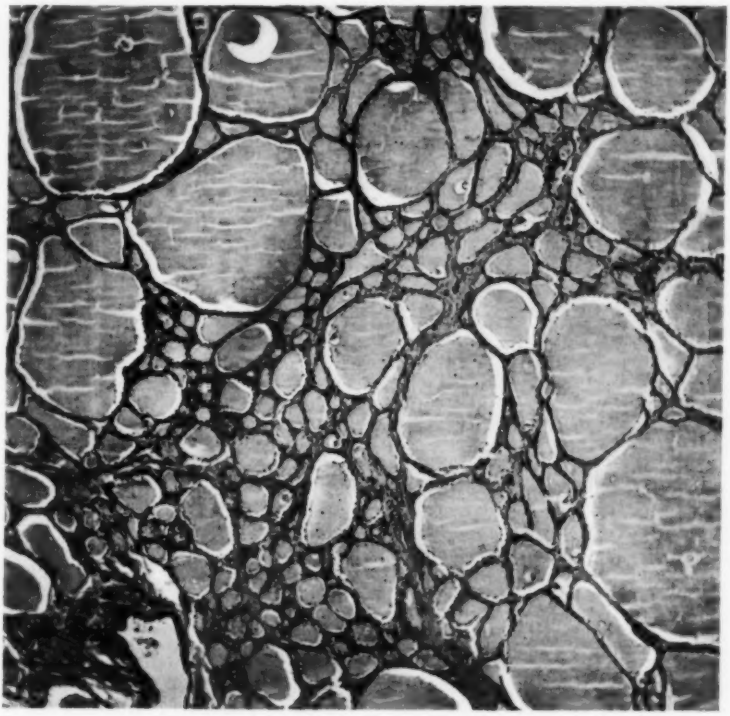

FIG. 1. *Case I.* Thyroid. × 250. Showing the thyroid follicles distended with old, rather granular colloid and lined with extremely flat epithelium. The epithelium is flatter than normal and the bulk is less than would be found in colloid goitre where the epithelium might be as flat.

peripheral edema. The thyroid gland was just palpable. Examination of the lungs revealed no abnormalities. The heart was somewhat enlarged. Retromanubrial dulness measured 5 cm., the right cardiac dulness 2 cm., in the fourth interspace and the left cardiac dulness 8 cm. in the fifth interspace. The aortic

second sound was accentuated but there were no striking auscultatory findings. There was evidence of peripheral vascular sclerosis and the blood pressure was 140/78 in both arms.

Laboratory examination revealed a slight secondary anemia. There was a hemoglobin of 77 per cent (Sahli), red blood cells 3,200,000, and a characteristic

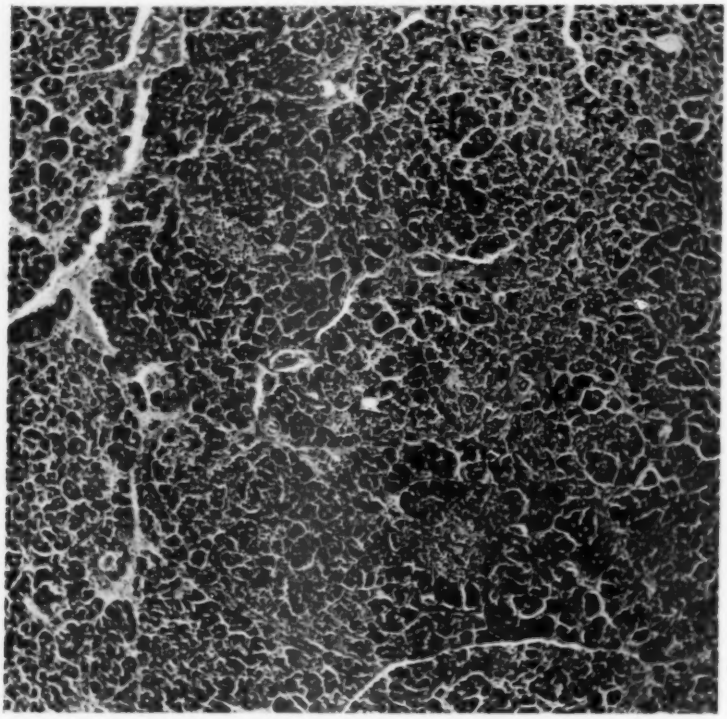

FIG. 2. *Case I.* Pancreas. × 250. Showing diffuse scarring of the parenchyma and hyaline deposits in the islets of Langerhans.

smear. The urine was of high specific gravity (1.026) and contained 19 grams of glucose per liter. There was no albumin or important sediment. There was a definite acetonuria. The blood sugar was 159 mgm. per cent, the non-protein nitrogen 33 mgm. per cent. The blood and spinal fluid gave a negative Wassermann reaction. The basal metabolic rate was −10 per cent.

The diabetes was regulated while he was on a diet containing a total of 1600 calories and 50 grams of carbohydrate and taking 20 units of insulin in two equal allotments.

Eighteen months later he was admitted in coma, there was hypoglycemia, and for the first time evidences of myxedema. The skin was found to be pale, dry, and definitely thickened. The hair was now dry and less in amount than before. The hypoglycemia was easily relieved and he was found to be capable of taking a diet containing a total of 1900 calories and 65 grams of glucose without the aid of insulin. The patient was lethargic, uninterested in his surroundings, and talked in a slowed manner. The rectal temperature was low and the pulse rate averaged 70 per minute. The basal metabolic rate was now found to be −30 per cent. The thyroid gland could not be felt. The degree of arteriosclerosis had become more pronounced and the blood pressure was at approximately the same level. There was now a harsh systolic murmur associated with a thrill over the aortic valve area and transmitted into the vessels of the neck. The heart was slightly larger than on the previous admission, a teleroentgenogram showing the following measurements, M.L. 10 cm., M.R. 4.5 cm., and a total internal diameter of the chest of 24.5 cm. The electrocardiogram showed an inversion of the T wave in lead one with a levogram predominant. There were no other striking changes in the laboratory findings.

Chart I shows the hospital course. When thyroid extract was administered the signs of myxedema ameliorated, but the diabetes became activated and signs of cardiac insufficiency developed. Accordingly, the extract was discontinued, and there was a return of the evidences of myxedema and a disappearance of the signs of altered carbohydrate metabolism.

He was followed for ten months and during this time the evidences of myxedema became more pronounced and the therapeutic attention required by the diabetes was negligible. He was then readmitted and died within a few hours with the symptoms and signs of congestive heart failure. There had been no evidence of the "myxedema heart" described by Zondek. At the pathological examination by Dr. W. G. McCallum, in addition to the arteriosclerotic aortic valvular heart disease, there was a markedly atrophied thyroid gland and hyaline degenerative changes in the greater number of the pancreatic islets of Langerhans of a small pancreas.

In this case there is presumptive evidence of the existence of diabetes for three years, and definite evidence of diabetes for two years before the symptoms and signs of hypothyroidism became of sufficient degree to be recognized. With the return of the metabolism toward normal limits under a thyroid-extract regime, the diabetes and cardiac insufficiency increased in severity, ameliorating with the discontinuance of the substitution therapy. Autopsy showed definite evidence of thyroid and pancreatic islet degeneration.

Case II. G. S. Unit 11,342. A Russian Jewess, 62 years of age, had been followed in the dispensary since 1907 chiefly for the treatment of an intractable leg ulcer which had its etiology in the marked varicose veins which were present. In 1915 a diagnosis of myxedema was made. At that time she complained of being cold. The speech was slowed and the voice gruff. The tongue was thickened, the skin dry, and the hair quite coarse. She was markedly overweight. From that time on she took varied amounts of thyroid extract at irregular intervals. In 1927 because of progressive weakness she was admitted to the hospital.

Her history showed that her parents had lived long, dying at the ages of 80 and 90. There had been no goitre or diabetes in the family. Although her mother had been obese there was no family tendency to gain excessively in weight. There had been twelve normal pregnancies. The menopause had occurred in 1915, with no severe symptoms. In 1915 she noticed a painless edema of the lower and upper extremities and of the face. Associated with the edema was susceptibility to cold and dryness of the hair. She noted that her voice was of deeper tone and she could not think as clearly as formerly. At this time the administration of thyroid extract was begun. She was convinced that while she was taking the thyroid extract her general condition was much improved and that the edema disappeared. Examinations of the urine had repeatedly been negative for glucose. A single blood-sugar determination in 1925 is recorded as 135 mgm. per cent.

On admission, March 31, 1927 she was seen to be a short, stocky female, 146 cm. in height and weighing 80 kilograms. The calculated ideal weight for one of her age was 58 kilograms. The facial expression was dull, the features were large, the nose broad and the lips very thick. The fingers were short and thick, almost spade-like. The skin was pale and somewhat yellow in color, parchment-like in character and there was a marked non-pitting thickening of the subcutaneous tissues. The hair was dry and coarse, the eyebrows almost absent and the axillary hair completely gone. The peripheral vessels were thickened and the arterioles of the retinae were narrow and tortuous. The heart was somewhat enlarged, the teleroentgenogram showing the following measurements: M. R., 5.5 cm., M.L., 10 cm. and total internal diameter of the chest, 26 cm. Other than an accentuated aortic second sound there were no auscultatory changes. The blood pressure was 155/110 in both arms.

The urine was normal in specific gravity, contained a trace of albumin but no glucose. There was no significant sediment. There was a mild secondary anemia with a hemoglobin of 77 per cent (Sahli), a red blood count 3,770,000 per c.mm. a normal total white blood count and a normal differential in the smear. The phenosulphonephthalein test for kidney function showed a 60 per cent excretion of the dye in two hours. The blood non-protein nitrogen was 30 mgm. per cent, the blood sugar 154 mgm. per cent. The blood Wassermann was negative. The x-ray photograph of the sella turcica showed it to be markedly increased in size. The visual fields were normal. The basal metabolic rate was −30 per cent. The electrocardiogram showed the T wave to be diphasic in all three leads, a negative P wave in lead 3, and a levogram predominant.

On a regimen of thyroid extract the metabolism rose to −1 per cent, the blood sugar to 256 mgm. per cent and 6 per cent glucose appeared in the urine. There was, however, marked subjective improvement and a decided change for the better in the manifestations of the myxedema. Because of the clinical improvement the patient was discharged on a maintenance allowance of thyroid extract even though it was at the sacrifice of a better regulation of the diabetes. She has been followed at intervals since, and the fasting blood-sugar is found to remain at a level of 150–170 mgm. per cent as long as the metabolism is low, but when the metabolism rises to normal limits the fasting blood-sugar increases to 300 mgm. per cent. She feels much worse at these times. The blood pressure remain at a constant level 140/100. In *summary* this patient showed evidences of myxedema for twelve years before diabetes was discovered. In her case there is a definite increase in the severity of the diabetes as the metabolism returns to normal on substitution therapy, although the association is not so striking as in the first case.

It is interesting to speculate why the patient with myxedema should be more susceptible to pancreatic insufficiency. Of the 22 patients with myxedema reviewed, 17 (77 per cent) were women, 82 per cent in the 40–60 year group. The majority were obese, a large percentage had arterial disease, the fruitful habitus for the occurrence of diabetes mellitus. None of these individuals showed glycosuria, and the tolerance to ingested glucose was increased in those in whom it was tested. One patient, a cretin weighing 100 pounds, showed no urinary sugar after the exhibition of 300 grams of glucose by mouth. The fasting blood sugar was normal or below normal in all the patients in whom it was determined.

Janney and Isaacson (10) demonstrated the frequent occurrence of hypoglycemia in cases of myxedema, but Gray (11) showed that after fasting the blood-sugar was as high in cases of myxedema as in patients with hyperthyroidism, and above normal levels. Gardiner-Hill (12) had 15 cases of myxedema with normal blood-sugars; Geyelin (9) also found normal blood-sugar levels in patients with myxedema; Brett, Smith, and Hill found the blood sugar at a low level, but the tolerance curve high and prolonged, and since no glycosuria was observed, they advanced the query of elevation of the renal threshold for glucose. Although there is no unanimity of opinion, the evidence seems to support the contention that patients with myxedema do have an increased tolerance to ingested glucose. When diabetes is combined with myxedema, does the mildness of the malady result from the pre-

domination of the increased glucose tolerance seen in cases of myxedema over the decreased tolerance found in instances of diabetes?

Burn and Marks (13) by a series of investigations demonstrated that the pancreatic action is subservient to the thyroid control, the liver glycogen remaining normal in amount. Hypoglycemic reactions following insulin are more severe when the liver glycogen has been shunted by splanchnic nerve section, the use of ergotamine, thyroidectomy, or after prolonged thyroid feeding had exhausted the liver glycogen. The hyperglycemic response to adrenalin is just the opposite, the blood-sugar not rising as high as normally. Farrar and Duff (14) disagree, however, in that they demonstrated that adrenalin would produce hyperglycemia even when preceded by ergotamine. Therefore in myxedema one would, by parallel reasoning, expect the lowering of the blood-sugar following insulin to be more marked than in the normal and the elevation of the blood sugar by adrenalin to be less marked. As a matter of interest very little is to be found on this phase of metabolism. DuBois (15) in his text investigated the low basal rates. Boothby (16) and his co-workers studied the nitrogen metabolism, and numerous observations have been listed merely as regards glucose tolerance tests. Two patients of this series were given 100 grams of glucose by mouth and three hours later 1 cc. of adrenalin (1/1000) subcutaneously; both showed glycosuria. No excretion of sugar in the urine followed the giving of glucose alone or adrenalin alone. Blood-sugar tests were not made as the procedures were carried out several years ago. As a matter of fact, one cannot rightly draw an analogy between the experiments of operative strumi-priva and myxedema, as the latter is no doubt something more than mere thyroid deprivation.

It is, of course, well known that other endocrine glands are linked with the increased reactivity to insulin. Geiling (17) and others demonstrated that completely hypophysectomized dogs, and also animals in which the "posterior lobe secretion" is absent or greatly diminished, are hypersensitive to insulin. They also showed that extracts of the posterior lobe of the pituitary gland protected these hypophysectomized animals against the hypoglycemia and convulsions attending the injections of insulin. The anterior lobe of the pituitary seemed to play no important rôle in this altered reactivity.

Britton (18), and his co-workers found increased sensitivity to insulin in animals that were deprived of the medullary portion of the adrenal glands. Harrop and Weinstein (19) also found this to be true in bilaterally adrenalectomized animals that were leading apparently normal existences with the aid of adrenal cortex extract (Pfiffner-Swingle). Patients with Addison's Disease (20) also showed evidence of increased sensitivity to insulin, although here the adrenal cortex is the deficient factor.

Why should the diabetes become more severe as the metabolism returns to normal levels under therapeutic adjustment? It must mean that the individual body cells are working at a new level and that when their metabolic exchange rate is increased their ability to respond is over-taxed. Mere raising of the metabolism is not enough, for Allen showed years ago that diseases which lower the body metabolism act favorably on the carbohydrate tolerance of a patient with diabetes, whereas fever, pregnancy, thyroxin, and adrenalin tend to elevate the metabolism and hence have an unfavorable influence on the course of the diabetes. The paradox is exercise which raises the metabolism, but has a favorable influence on the diabetes. This is, however, an acute elevation in contrast to the sustained metabolic changes present in the other conditions. Patients with myxedema have low basal metabolisms, are very lethargic, exercising little, but their appetites are usually small, so that the pancreas is perhaps protected by the resulting lowered carbohydrate intake. Wilder (4) concluded that in instances where the metabolism is elevated tissue cells require more insulin, disproportionally greater in amount than when the metabolism is low.

That individuals may have low basal metabolisms that are normal for them has been repeatedly emphasized by W. O. Thompson (22) and his co-workers. They have demonstrated the inadvisability of giving these patients thyroid extract, since the level of the metabolism is raised at the expense of the patient's well-being.

The polyglandular phase should be considered. Many of the cases must no doubt have a great hypopituitary element, but decreased tolerance is often seen in these cases. Cushing (21) stated that normal posterior-lobe activity is essential to effective carbohydrate metabolism and later reported that 12 per cent of his cases of acromegaly

showed true diabetes mellitus. With the prevalent ubiquitous administration of thyroid extract to these polyglandular dyscrasias it is surprising that more, perhaps latent, diabetes is not revealed.

It is rather evident that cases of diabetes mellitus and myxedema should do badly when the metabolism is elevated by the use of thyroid extract. These cases have become adjusted to low metabolic levels and although our therapeutic supervision raises their metabolism to our accepted normal group levels, for them it is comparatively a decided elevation and the end-result is hyperthyroidism and diabetes mellitus.

It is important to emphasize that in the first case reported the diabetes was diagnosed first, and months later evidences of myxedema were discovered. In the second case the reverse was true, a diagnosis of myxedema being made twelve years prior to the discovery of the diabetes. The occurrence of two cases of diabetes among twenty-two individuals with myxedema is of striking frequency when one considers that only two of the three thousand patients with diabetes also suffered with myxedema.

In 6 of the 10 cases reviewed the diagnosis of diabetes antedated the appearance of the myxedema, while in 4 of the patients the evidences of myxedema were primary. Regardless of the order of appearance the diabetes seemed to be definitely modified by the untreated myxedema and to be decidedly intensified when the myxedema was attacked with thyroid extract.

It is interesting to read a report by Rohdenburg (23) in 1922 entitled "A Case of Spontaneous Disappearance of Diabetes." It is the record of a Russian Jewess who had symptoms of diabetes mellitus and a glycosuria present 10 years prior to the menopause which occurred at the age of 40. Two years after the climacteric repeated examinations of the urine failed to show sugar and she was able to eat candy without having glucose appear in the urine. A year later there was a generalized boggy edema of the subcutaneous tissues, "general harshness of the skin," dyspnea, and vertigo. Members of her family had noted mental deterioration. The blood pressure was elevated and there was an associated hypertrophy of the heart. The urine contained albumin and casts. The patient died in coma, thought to be nephritic in origin.

At autopsy the lesions of interest were found in the pancreas and thyroid. Sections demonstrated almost complete destruction of the secreting alveoli of the thyroid with a replacement by connective tissue. The pancreas showed fibrotic destruction of the glandular elements in the region of the head, and a marked hypertrophy of the islets of Langerhans in the body of the organ.

Rohdenburg regrets that he did not have the opportunity of conducting a more detailed study of the case.

It is quite conceivable that this patient had diabetes mellitus and that the signs and symptoms of the disease disappeared as she developed evidences of the thyroid deficiency which were later proved at autopsy.

In general the treatment rests upon the decision as to whether the patient is more comfortable when active and on a regime including thyroid extract and dietary restriction, or when less active, but with an unrestricted diet. A moderate amount of each type of substitution therapy seems to offer the best method of handling this type of case.

SUMMARY

1. The literature on the combination of myxedema and diabetes mellitus is investigated with the collection of a total of ten cases.

2. Two cases, one with necropsy data, are added.

3. Certain hypotheses as to the etiology and pathological physiology of the malady are reviewed.

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TUBERCULOUS INFECTION IN MEDICAL STUDENTS

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The question of tuberculous infection in medical students has aroused great interest for many years. It will be admitted that medical students, during their clinical years, are subject to greater exposure[1] than are other persons of similar age and social status, such as, for example, students in other professional schools. However, it is not established that exposure in adult life, *per se*, is the deciding factor in the development of tuberculosis, although this may be the case. On account of their age alone and without any excessive exposure, tuberculosis would be expected to be the most important cause of disability and of death among medical students. The matter will not be settled until adequate statistics are available, not only for this particular group, but for a comparable control population.

The object of the present report is to summarize present knowledge of the subject and to present certain observations which have been made on students of medicine in the Johns Hopkins University for whose medical supervision one of us (N. B. H.) has been responsible since 1926. The work of the John J. Abel Fund for Research on the Common Cold has helped to make this supervision unusually close, since during the academic year 1928–1929 approximately two-thirds, and during the years 1929–1931 practically all of the students were currently reporting all respiratory illnesses. Supplementary data are

[1] In this connection comparative mortality rates from pulmonary tuberculosis for various occupations are of great interest, but unfortunately such are not available for the United States. Data for England and Wales indicate that registered physicians have a higher mortality than certain other professional classes, for example, clergymen, barristers and bank officials, but still only about one-half that suffered by "All occupied and retired civilian males." (The Registrar-General's Decennial Supplement. England and Wales. 1921. Part II: Occupational Mortality, etc.)

also presented from the University of Michigan and from Western Reserve University.

TUBERCULOSIS MORBIDITY IN VARIOUS ADULT POPULATIONS

Various estimates have been made of the frequency of tuberculosis in the general population. Based upon the Framingham experience, Armstrong (1) estimated, as a rough average for all ages, nine or ten active cases of pulmonary tuberculosis to each annual death. Since in the United States Registration Area for Deaths the annual death rate from pulmonary tuberculosis is in the neighborhood of 1 per 1000 for the age group 20–29 years, this would mean that approximately 1 per cent of the population of this age group have active tuberculosis at any one time.

It is worth noting also that, in the report on physical defects found in drafted men aged 18–30 years, Love and Davenport (2) state that approximately 3 per cent were rejected on account of definite or suspected pulmonary tuberculosis. It should be remembered, however, that the death rate from the disease has declined considerably since 1917.

In a study of the records of the Life Extension Institute, Sydenstricker and Britten (3) found that, among males aged 20–24 years, approximately one and a half per cent had definite or suspected pulmonary tuberculosis. Those examined were selected physically and economically, since they had been able to pass an examination for life insurance and to pay the premiums. There is a further objection which the authors express thus: "It must be recognized that some persons accept this service to find out what is wrong with them because they know or think that something is wrong."

Judging from such inadequate data, the best estimate which we can make at the present time is that in males of from 20–29 years in the general population, the proportion with symptomatic tuberculosis at any one time is probably not lower than one and not higher than three per cent.

No reliance can be placed on *annual* morbidity rates for the general population of any area save to consider that such represent minimal incidence. For special groups, however, valuable records are available. In the United States Army (4), for example, the morbidity rate for all forms of tuberculosis was 2.72 per 1000 in 1927 and 2.69 per 1000 in 1928. In the Navy (5) the rates for the same years were 2.49 and 2.19, respectively. The data are not classified according to age groups.

PULMONARY TUBERCULOSIS AT THE UNIVERSITY OF MICHIGAN

The University of Michigan has conducted a Health Service for students for more than fifteen years, and Dr. Forsythe, Director of the Service, has kindly furnished us with data on the known incidence of pulmonary tuberculosis in various departments (table 1).

As shown in table 1, medical students at the University of Michigan

apparently present a higher incidence of tuberculosis than students in other departments. However, from a statistical viewpoint the differences between the rates for the different schools are not significant, and a longer period of observation is necessary to determine the facts. The figures do not cover complete calendar years, and rather strict diagnostic criteria have been used. It is unfortunate that similar statistics covering a period of years are not available for other universities.

TABLE 1

Incidence of pulmonary tuberculosis in various schools of the University of Michigan for fourteen academic years, 1917–18 to 1930–31. (Summer sessions excluded)

ITEM	DEPARTMENT					
	Literature	Law	Dentistry	Engineering	Graduate	Medicine
Student-years of exposure	60,310	5,435	4,245	21,011	5,537	6,755
Cases of tuberculosis	105	10	9	50	14	19
Incidence per 1,000 student-years	1.74	1.83	2.12	2.38	2.52	2.81

MORBIDITY EXPERIENCED AT THE WESTERN RESERVE SCHOOL OF MEDICINE

At the Western Reserve School of Medicine, with which one of us (J. A. D.) is now associated, the reason for withdrawal of students has been carefully recorded by Miss Frances Hunter, Registrar, since 1923. The average annual enrollment has been approximately 250. Through the courtesy of Dr. L. H. Ferguson, supplementary data have been provided for cases of tuberculosis occurring since the establishment of the Student Health Service in 1927. During the eight years from October 1, 1923, to September 30, 1931, there have occurred 11 cases of pulmonary tuberculosis and pleurisy with effusion, including one case discovered a few days after initial registration. Two of these students have died, one from tuberculous meningitis. Of eight from whom the necessary statements were obtained, three are known to have had active pulmonary tuberculosis before admission to the medical school. Included in the three is the student who died of tuberculous meningitis.

MORBIDITY EXPERIENCED AT THE JOHNS HOPKINS SCHOOL OF MEDICINE

During the five years from October 1, 1926, to September 30, 1931, there have occurred 10 cases of pulmonary tuberculosis (including pleurisy with effusion) among Johns Hopkins medical students. Of these student none has died. The average annual enrollment during this period has been approximately 250. Detailed records are available for all save one student (Case 2) who entered the medical school in 1926 after two years in a sanatorium, but who broke down and was forced to withdraw in his first year of residence.

Case 1. (C. S. T.) W. M. Age at onset, 23 yrs. No personal or familial history of tuberculosis. On adm. to M. S. (Oct., 1924) phys. exam. was neg.; no X-ray of chest; no tuberculin test. 11-28-26, following unusual exercise, noted soreness in rt. upper chest. 12-2-26, P. E. neg. About 12-12-26 noted headache, feverishness and pain localized to right border of sternum. 12-15-26, X-ray report: "Remains of pleurisy at rt. base." 12-16-26, adm. hospital with physical signs of pleural effusion, rt. chest, T. 101.7°F. 12-21-26, X-ray report: "Huge pleural effusion, rt. side." Patient treated at Maryland Tuberculosis Sanatorium Jan. to Sept. 1927 (8 mos.), gaining 33 lbs. 10-1-27, re-entered M. S. 12-1-27, X-ray report: "Lungs clear, no evidence of pleurisy." Completed studies without interruption, graduating in June 1929. Enjoying good health, 12-17-31.

Case 3. (C. C. S.) W. M. Age at onset, 21 yrs. Personal history neg. Maternal grandparents had tuberculosis but pt. was never exposed. On adm. to M. S. (Oct. 1928) P. E. was neg. 10-25-28, X-ray report: "Lungs clear." No tuberculin test. Had three upper respiratory attacks between 9-30-28 and 3-5-29. About 1-15-29, patient began to feel unusually tired and somewhat feverish in the late afternoon. From 2-15-29 to 2-25-29 afternoon the temperature was usually 99.6°F. 2-24-29, noted sharp pain in left axillary region accentuated on deep inspiration; had headache and slight fever (99.6°F.). No abnormal physical signs but X-ray report at this time stated: "Soft infiltration left apex, probably tuberculous in origin." 3-2-29, P. E. disclosed a few moist râles in left supraspinous fossa brought out by coughing. Pt. entered Trudeau Sanatorium 3-15-29, did very well there and re-entered M. S. 12-1-30. At present in good health, 12-17-31.

Case 4. (W. O. K.) W. M. Age at onset, 22 yrs. No personal or familial history of tuberculosis. On adm. to M. S. (Oct. 1927) P. E. was neg., save for chronically infected tonsils. 2-29-28, X-ray report: "Lungs clear." 3-12-28, X-ray report: "Lungs clear." No tuberculin test. 11-1-28, patient had an acute upper respiratory infection (? influenza) of 3 weeks' duration; lost 7 lbs. Cough persisted and on 12-2 either a new invasion or a relapse occurred and pt. was in

hospital between 12-3 and 12-12. Cough persisted and on 1-4-29 he came down with another severe cold; nasal symptoms cleared up but cough with slight mucoid expectoration continued. 3-28-29, had tonsils removed, convalescence normal. 5-2-29, P. E. neg., save still below usual weight. X-ray report: "Soft infiltration beneath left clavicle, probably tuberculous." 5-2 to 5-9 took temperature several times daily; no fever. 5-9-29, brought to laboratory small amt. of muco-purulent sputum which contained tubercle bacilli. Physical examination disclosed few fine moist râles in left supraspinous fossa. 5-19-29, entered Trudeau Sanatorium; did well for several months but relapsed. Still in Sanatorium, 12-17-31.

Case 5. (S. E.) W. F. Age at onset, 23 yrs. Had pleurisy with effusion at age of 12 years. Father died of pulm. tbc. at 44 years. Brother had mesenteric tuberculosis but recovered. On adm. to M. S. (Oct. 1927) P. E. disclosed impairment of resonance with diminished breath sounds at right base posteriorly. 11-7-27, X-ray report: "Bronchitis and emphysematous type of chest." 5-10-28, X-ray report: "Lungs clear; slight pleurisy at rt. base." No tuberculin test. Pt. subject to colds; had 4 upper respiratory attacks between 9-30-28 and 6-1-29. 9-16-29, while in London, pt. had a slight hemoptysis. 9-26-29, entered Calydor Sanatorium. Was very ill for about a year but during 1931 made steady improvement.

Case 6. (W. K. W.) W. M. Age at onset, 29 yrs. No personal or familial history of tuberculosis. On adm. to M. S. (Oct. 1926), P. E. neg.; no X-ray. Pt. subject to colds; had 4 upper respiratory attacks between 9-30-28 and 6-1-29. 11-26-28, X-ray report: "Lungs clear." 3-4-29, X-ray report: "Lungs clear except for increased root infiltration." 1-27-30, Mantoux test (0.1 mgm.) markedly positive. Nov. 1929, had sore throat, cough and hoarseness and P. E. disclosed few transient râles in left axilla; pt. deferred X-ray. Jan. 1930, began to feel unusually fatigued in late afternoons. 1-27-30, X-ray report: "Soft infiltration both apices, suggesting active tuberculosis." 2-4-30, went to Trudeau Sanatorium. He has progressed very favorably but is still at Saranac.

Case 7. (G. L. W.) W. M. Age at onset, 23 yrs. No personal or familial history of tuberculosis. On adm. to M. S. (Oct. 1927) P. E. neg.; no X-ray. Pt. not very susceptible to colds, reporting only two between 9-30-28 and 9-27-30. 2-3-30, marked positive Mantoux test (0.1 mgm.) with slight constitutional symptoms. 2-6-30, X-ray report: "Increased infiltration root zone and bronchial tree; no calcified glands." 5-30-30, was taken suddenly ill with pain in rt. chest and fever (105°F.), with rapid appearance of effusion on rt., chest being tapped twice in first week of illness; fever continued high until 6-15 and pt. was not completely afebrile until Oct. 1930. Oct. 1931, re-entered M. S., chest clear save for signs of thickened pleura, rt. base. 10-14-31, X-ray report: "Pleural effusion, rt. base; some infiltration of apex." Pt. seems in good health (12-17-31).

Case 8. (C. F. S.) W. M. Age at onset, 24 yrs. Personal history neg., save for chronic hawking cough with scanty mucoid sputum; F. H. neg. On adm. to M. S. (Oct. 1928), P. E. neg., save for old infection of both antra, confirmed by X-ray. Pt. is rather susceptible to colds, reporting 7 between 9-30-28 and 11-29-30. 10-11-28, X-ray report: "Increased infiltration bronchial tree." At intervals while in M. S. pt. suffered from nagging pain in right or left axilla which persisted from a few minutes to 4 or 5 days, but was never associated with fever or cough. 1-20-30, Mantoux test (0.1 mgm.) essentially negative; slight stain at site of injection; no infiltration. During Oct. 1930 he gained 6 lbs. Nov. 1930 pt. noted unusual feeling of fatigue in afternoons. About 11-15-30 sputum changed in character, becoming more abundant and muco-purulent. 11-22-30, pt. had night-sweat but stated that he was sure he had had no fever prior to this time. 11-22-30, X-ray report: "Areas of soft and fibroid infiltration upper lobe each lung, particularly left." 11-23-30, sputum positive for tubercle bacilli. Pt. was admitted to Trudeau Sanatorium early in December, 1930. To the present his progress has not been satisfactory.

Case 9. (E. T. W.) W. F. Age at onset, 27 yrs. No personal or familial history of tuberculosis. On adm. to M. S. (Oct. 1927) P. E. was neg. Pt. moderately susceptible to colds, reporting 10 between 9-30-28 and 4-19-31. 5-10-28, X-ray report: "Slightly increased fibrosis of bronchial tree; few calcified glands, root zone." 2-10-30, Mantoux test (0.1 mgm.) positive. March 1931 pt. had a "cold" with slight fever and weakness of three or four days' duration; returned to classes but did not feel up to par. Caught another "cold" at Easter. About 4-10-31, noted pain in rt. chest, most marked on deep inspiration; this pain continued and pt. had night sweats, but no cough or loss of weight. 4-18-31, T. 99.2°F.; impaired resonance and friction rub, rt. base posteriorly; X-ray report: "Probable beginning pleural effusion at rt. base." Pt. adm. to J. H. H. X-ray taken several days later showed frank effusion on rt. side. 5-7-31: Sent to Trudeau Sanatorium where she has made steady improvement.

Case 10. (E. V. F.) W. M. Age at onset, 25 yrs. No personal or familial history of tuberculosis. On adm. to M. S. (Oct. 1928) P. E. was neg. Pt. reported only 6 colds in 3 years, 9-30-28 to 10-10-31. 10-17-28, X-ray report: "Lungs clear." 12-2-29, Mantoux test (0.1 mgm.) strongly positive, with slight constitutional reaction. 1-24-30, X-ray report: "Lungs clear, slight root infiltration." Pt. enjoyed good health until August, 1931, when, while working in a hospital in R. I., he noted slight pain in rt. chest about level of 3d and 4th ribs near the sternum, which was not affected by respiration. X-ray disclosed an extensive, rather soft infiltration extending from the mediastinum into the rt. lung. P. E. neg. at this time. October 1930, X-ray showed extension of infiltration. Adm. to J. H. H. and was examined by many members of the staff, but no outspoken abnormal physical signs were detected. Pt. had no fever. It was felt that the case was one of tuberculosis of a type rather unusual in the adult.

Yet the case can hardly be of the first infection type, since the pt. had a positive tuberculin test some 20 months previously. 11-1-31. Sent to Trudeau Sanatorium.

These cases show several interesting features. Only one patient (No. 5) gave a history of familial exposure to tuberculosis. Excepting patient No. 2, only one (No. 5) gave a history which might be interpreted as a prior attack of pulmonary tuberculosis. The remaining eight students were in good health on admission and, in seven of these, x-rays of the chest had been taken prior to onset and had shown no evidence of active tuberculosis. One case (No. 4) may have a relation to an attack of influenza in November 1929. Previous reaction to tuberculin is known in four instances: three had a positive Mantoux test, one 20 months, the second 14 months, and the third 4 months before onset of symptoms. One had been negative to the Mantoux test (0.1 mgm.) nine months prior to earliest symptoms.

Among the nine regarded as tuberculous and developing in the Medical School, there are included 3 cases of pleurisy with effusion, 5 cases of apical disease of the adult type and 1 case with a type usually regarded as peculiar to childhood.

The tuberculosis record of the Johns Hopkins Medical School in the past few years would appear to be very similar to that of Western Reserve. As already noted, the enrollment in the two schools is approximately the same. The average age of the students is also about the same. The Johns Hopkins students, however, are representative of a far wider geographical area. If it be permitted to combine the experiences of the two schools, we have an experience of approximately 3250 student-years ($250 \times 5 + 250 \times 8$) with a total of 21 cases, with the high average annual morbidity rate of 6.5 per 1000. Of these 21 students, 6 dropped out during the first year of residence, 2 during the second, 7 during the third and 6 during the fourth year.

ACTIVE TUBERCULOSIS IN STUDENTS AS REVEALED BY SPECIAL SURVEYS

So far in this report we have been discussing the incidence of tuberculosis as revealed by methods in which the first line of detection or "screen" has been physical examination. Statistics obtained in this way can never be compared with those relating to tuberculosis as disclosed by diagnostic methods in which the x-ray is used as the primary screening instrument. The most thorough study of the latter

type is that of Hetherington, McPhedran, Landis and Opie (6) of the University of Pennsylvania. Both college and medical students "were given intracutaneous tuberculin tests, stereoscopic roentgenological examination of the chest, and when the latter revealed tuberculosis, physical examination." All reported as active cases had symptoms or physical signs in addition to x-ray findings Among 279 college (non-medical) students, of an average age of 19.3 years, only one active case was discovered. Among 452 medical students of an average age of 23.6 years, however, 14 cases were discovered, distributed as follows: one among 98 in the first year; none among 103 in the second year; four among 129 of the third year, and nine among 122 fourth-year students.

At the Western Reserve Medical School in 1930, Dr. T. Wingate Todd took flat x-ray films of the chest on 75 students shortly after admission to the first year. One case of active disease with physical signs was discovered. During the current session (1931–32) also, 40 third-year medical students have had flat films of the chest taken by Dr. David Steel and one active case has been discovered. The 40 are thought to be a fair sample of the class, although in the remaining 20 third-year students there is known to be one arrested case.

At the Johns Hopkins Medical School, since 1928, flat films of the chest have been taken on all students on initial enrollment, as a supplement to the usual physical examination. To 1930, inclusive, no active case of tuberculosis was discovered among 220 entering students. Unfortunately, no systematic x-ray survey comparable to that of the University of Pennsylvania has been made of the upper classes. However, many of the students have had chest films taken on enrollment as volunteers under the John J. Abel Fund, or during an acute upper respiratory attack subsequent to enrollment. No case of active tuberculosis was discovered among 50 second-year volunteers, but among 44 students of the third and fourth years, two cases were found.

A higher incidence of pulmonary tuberculosis in upper than in lower medical classes may be apparent rather than real. Persons sick with tuberculosis will rarely apply for admission to a medical school, or if they do, they will probably be excluded on physical examination. First-year classes, therefore, represent a group from which cases ordinarily present have largely been excluded. Also, there is a tend-

ency for those who are taken ill during their course to continue their studies, if possible, which might result in an accumulation of cases in the fourth year.

LATENT APICAL TUBERCULOSIS AMONG STUDENTS

In the above-mentioned study, Hetherington, McPhedran, Landis and Opie (6) found apical infiltration, unassociated with physical signs or symptoms, in 3.2 per cent of college students and in about the same proportion of first-year medical students. In the second, third and fourth year medical classes, however, the average incidence was 11.6 per cent, with no appreciable difference in frequency as between the classes. It was noted, however, that "Conspicuous pulmonary infiltration extending below the clavicle was not found in students of the first two years, but occurred in 6 medical students of the third year and in 13 of the fourth year."

Among the 40 third-year medical students examined at Western Reserve by Dr. Steel only two presented evidence of latent apical infiltration. One of these had been a contact of his father who had died from pulmonary tuberculosis but the student had never had any recognized tuberculosis himself.

At Johns Hopkins, among 220 first-year students, 11, or 5 per cent, were found to have apparently healed apical lesions. Among 50 second-year students there were two such cases and in the third and fourth years 5 were found among 44 examined.

Obviously further data are necessary. From the findings of Hetherington, and others, it would appear possible that gross tuberculous lesions may develop in medical students and become arrested without causing withdrawal from classes. It is pertinent to note here that at Johns Hopkins no student known to have "latent apical" tuberculosis has developed signs of activity. Two such persons have been under observation for four years, 6 for three years, 8 for two years and 2 for one year.

CALCIFICATION IN LUNGS OR LYMPH NODES

In the University of Pennsylvania studies, areas of calcification in lungs or lymph nodes are reported in 44 of 279 college students (non-medical), or 15.8 per cent; and in 93 of 279 medical students, or 20.6

per cent. Since such calcification is considered to represent tuberculous infection usually acquired in childhood, this indicates the possibility that the medical students in that University are drawn from a stratum of society more exposed in childhood than the college group.

Among Johns Hopkins medical students presence or absence of calcification is recorded for 278 individuals, 176, or 63 per cent, being positive. The films have been carefully reviewed by one of us (F. H B.) and those in which calcification is doubtful have been excluded.

RESULTS OF THE TUBERCULIN TEST IN MEDICAL STUDENTS

In the winter of 1929–30 the Mantoux test was applied to practically all students in the Johns Hopkins School of Medicine, and in the fall of 1930 all new entrants to the school were tested. The tuberculin

TABLE 2

Tuberculous infection among medical students: Results of Mantoux test (0.1 mgm.), by classes

CLASS	NUMBER		PER CENT POSITIVE
	Tested	Positive	
First year	137	78	56.9
Second year	68	53	77.9
Third year	62	58	93.5
Fourth year	47	43	91.5
Total	314	232	73.9

was prepared and standardized by Dr. H. S. Willis of the Henry Phipps Institute of the Johns Hopkins Hospital. The dosage used was 0.1 cc. of a 1:1000 dilution of O. T. (0.1 mgm). Of 314 students tested, 232, or 73.9 per cent, were positive. A tabulation of the results according to classes is given in table 2.

As shown in table 2, a striking difference is apparent as between the third and fourth year students, and those of the first and second years. Also, the second year class shows a higher proportion of positives than the first year.

The first question which arises is whether the lower and upper class men are strictly comparable to one another in respect to factors which conceivably might influence their allergy to tuberculin. A change in

policy of the school, for example, which tended to admit more students from rural areas than formerly, might offer an explanation.

No change which conceivably could have this effect has taken place. The students of the first and second years were drawn from colleges and universities scattered pretty well over the United States, just as were those of the higher years, and both groups include a few from foreign countries. As a further check, the students were classified according to size of community in which they had spent the first fifteen years of life. Those who had spent this entire period in places of under 10,000 population were classed as "rural," while if they had lived exclusively in larger places they were classified as "urban." Those whose early years were divided between urban and rural areas were classed as of "mixed" upbringing. A tabulation on this basis revealed the fact that 27.8 per cent of the first and second year classes had spent their childhood exclusively in the country as compared with 39.4 per cent of those of the third and fourth years. Inasmuch as this factor is of influence, therefore, it would be expected to result in a lesser frequency of positives in the upper years at the time of admission than was found in the present first and second years.

Differences in age as between the classes can hardly be of importance. The median age of first-year students at time of testing was 22 years and 2 months, while that of those of the fourth year was 25 years and 2 months.

Individual instances of the acquirement of allergy by medical students are common. Recently, J. A. Myers (7) has cited several examples. Frequently such individuals are known to have been in contact with tuberculous patients, as in instances described by that author. A student under Dr. Herman's care was tested on 10-5-28 intradermally and found negative up to 1 mgm. O. T. During the summer of 1929 she worked in a sanatorium for two months making physical examinations of patients. She developed a keratitis in the fall of 1929 and had a marked positive reaction to 0.1 mgm. In other cases no such history can be elicited. A first year student at Johns Hopkins, for example, was negative to 0.1 mgm. on 11-12-29. Two months later, to the same dose and without having had any known contact in the interim, he had a marked positive reaction with adenitis of axillary glands and slight constitutional symptoms.

It has not as yet been possible to follow into the clinical years the first-year students with negative tuberculin reactions in order to demonstrate the fact of the acquirement of allergy in a large number of individual cases. However, a small number have been retested, 15 as late as one year after the original test. At the end of two months 4 of 51 tested had become positive. No change was observed in the reaction of 20 tested at the expiration of six months. At the end of a year 2 of 15 tested had become positive. If the 47 negatives remaining at the end of two months had all been tested at the end of a year, some 6 or 7 positives presumably would have been found, a total change in the year of about 20 per cent.

Of 14 negatives of the second, third and fourth years tested from three to five months after the first test, all were still negative to 0.1

TABLE 3

Results of retesting (Mantoux, 0.1 mgm.) of first-year negatives

INTERVAL FROM FIRST TEST	NUMBER RETESTED	NUMBER POSITIVE
2 months	51	4
6 months	20	0 } 6
12 months	15	2

mgm. And of 4 second-year men tested approximately one year from the first test, one only had become positive.

Pertinent also is the fact that in the upper classes a number of reactors had slight constitutional disturbances following the test. In the first year none such were noted. Also, the area of infiltration as observed at the expiration of 48 hours was substantially greater in the upper classes than in the first year. The average diameter (largest) of infiltration was for the former 20.3 mm. and for the latter 14.9 mm. (table 4).

Applying the term "negative" only to students who fail to react to an intracutaneous dose of 0.1 cc. of 1:100 (1.0 mgm.), Hetherington, McPhedran, Landis and Opie (6) found a similar trend but a much smaller difference between lower and upper classes in the University of Pennsylvania Medical School. Their proportions of positives are as follows: first year, 85 per cent; second year, 94 per cent; third year, 96 per cent and fourth year, 98 per cent. Among the college students

(non-medical) the proportions of positives were found to be 82.6 per cent for the first and second years and 89.4 per cent for the third and fourth years.

Heimbeck (8) has reported that in the Ullevål Hospital in Oslo, "56 per cent of the students gave a positive Pirquet reaction before they began their clinical work at the hospital, but after two years of hospital work there were 98 per cent of positive cases." This hospital, which has a total of 1500 beds, ordinarily has about 300 cases of tuberculosis under treatment. For the most part these cases are of the advanced type and are segregated in three special wards. However, it is stated that there are also cases of tuberculosis under treatment in other departments of the hospital.

TABLE 4

Extent of inflammatory infiltration following Mantoux test (0.1 mgm.) in first-year classes as compared with others

CLASS	NUMBER OF 48-HOUR OBSERVATIONS	AVERAGE DIAMETER	P.E.
		mm.	
First year	75	14.9	±0.39
Second, third and fourth years	141	20.3	±0.44
Difference		5.4	±0.58

It was surprising to us to find such a high proportion of first-year students at Johns Hopkins relatively anergic to tuberculin in that they failed to react to 0.1 mgm. At Western Reserve Medical School, however, in 1930, the proportion positive to 0.1 mgm. in the first year, 58.1 per cent, was almost the same as at Johns Hopkins.

It was also unexpected to find a considerable increase in the frequency of positives in the second year, before there had been any considerable opportunity for exposure to patients, the factor on which Heimbeck (8) and Myers (7) lay such great emphasis Further data are required, but the Baltimore and Philadelphia results, although based upon small numbers, indicate that a considerable proportion of medical students either acquire allergy or become more sensitive to tuberculin before completion of their second year.

It is, of course, not maintained that students failing to react to 0.1

mgm. of tuberculin intracutaneously have never been infected with tubercle bacilli. In the first place, experience has shown that individuals negative to this amount may react to a higher dosage. Thus among individuals 12–19 years of age, Hetherington, McPhedran, Landis and Opie (9) found that approximately 40 per cent of those negative to 0.1 mgm. would respond to 1.0 mgm. If this figure be applicable to first-year medical students, the proportion of positives to 1.0 mgm. at Johns Hopkins and Western Reserve would be somewhere in the neighborhood of 75 to 80 per cent.

Secondly, certain persons with definite areas of calcification, presumably due to tuberculosis, may fail to react to considerable doses of tuberculin. This is true even among children and is commented on by McPhedran (10) as follows: "The tuberculin reaction is often negative to 1.0 mgm. even in the event of large calcified nodules."

Among Johns Hopkins medical students, of 76 negative to the tuberculin test (0.1 mgm.), 44, or 57.9 per cent, showed evidence of tuberculous lesions on x-ray, three having localized apical infiltration.

Accepting as evidence of tuberculous infection either a positive tuberculin reaction (0.1 mgm.) or a lesion disclosed by x-ray, the proportions of infected medical students at Johns Hopkins according to classes are as follows: first year, 79 per cent; second year, 91 per cent; third year, 100 per cent, and fourth year, 98 per cent.

CONCLUSIONS

1. At present there is insufficient evidence to prove that medical students suffer a higher incidence of pulmonary tuberculosis than persons of similar age and economic status engaged in other occupations. Such data as are available, however, suggest that the student of medicine may be subjected to a higher risk.

2. On admission to the medical school, approximately 40 per cent of students are negative to the Mantoux test (0.1 mgm.), both at Johns Hopkins and at Western Reserve Universities.

3. A large proportion of such negatives (57.9 per cent in Baltimore) show evidence of calcification on x-ray of the chest, and are believed therefore to have been previously infected with the tubercle bacillus.

4. Judging from the proportions of students in various classes reacting to the test, and from the degree of inflammatory infiltration

observed in different classes, it is concluded that if a student is negative to tuberculin on enrollment he is practically certain to be positive before the completion of his third year. If he is only moderately allergic on admission, he is likely to become more sensitive to tuberculin with residence in the medical school.

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BOOK REVIEWS

Physical Diagnosis. By RICHARD CABOT, M.D., Professor of Clinical Medicine in Harvard University. Tenth Edition, Cloth. Pp. 529 with six plates and 279 figures. (*New York, Wm. Wood and Co., 1930.*)

In this latest edition of his book Dr. Cabot has added new material concerning coronary disease, electrocardiography, cancer of the lung, "cardiac asthma," toxic hepatitis, and encephalitis lethargica. The fact that this volume occupies a leading position among the texts on this subject is fully justified by its succinct presentation of such an amazing amount of fundamental information.

In all editions the author has wisely "endeavored to break down the false distinction between clinical diagnosis and laboratory diagnosis." At the same time he is conservative in recommending examination by special methods to the neglect of careful physical examination.

The numerous illustrations are, for the most part, well chosen. Exception might reasonably be taken to Figure 88 (after Lewis) in which the schematic representation of auricular fibrillation follows the old "multiple foci" theory in place of the now almost universally accepted "circus movement." Finally, while recognizing the limitations of space in such a book, your reviewer feels that more might well be devoted to a description of the *normal.*

E. C. A.

Clinical Electrocardiography. By SIR THOMAS LEWIS, M.D., F.R.S., D.Sc., LL.D., F.R.C.P., C.B.E., Physician of the Staff of the Medical Research Council; Physician in charge of Department of Clinical Research, University College Hospital; Honorary Consulting Physician to the Ministry of Pensions; Consulting Physician, City of London Hospital; Fellow of University College, London. Fifth Edition. (*London, Shaw & Sons Ltd., 7 & 8 Fetter Lane, E. C. 4, 1931.*)

Sir Thomas Lewis' elementary volume upon Clinical Electrocardiography, long well known, is now in its fifth edition. It still remains in our opinion the most satisfactory text available for outlining the principles of interpretation of the cardiac irregularities. In this edition Sir. Thomas has added discussions of one or two subjects, not included in the earlier editions. One wishes, perhaps, that he had discussed certain phases concerned with bundle-branch-block lesions and the interpretation of coronary thrombosis more in detail. There is no statement as to the correct interpretation of right and left bundle-branch curves. It is to be regretted that the curves illustrating coronary thrombosis should be marred by the induced current so plainly to be seen in the photographic reproduction. As an introduction into the subject of clinical electrocardiography, we know of no

text which explains so complicated a subject in so simple and clear a way. The volume is essentially only what it is meant to be, a simple and elementary guide to the interpretation of clinical records. For an exhaustive discussion of the subject in English, one turns naturally to Sir Thomas's larger volume on the mechanism of the heart beat.

E. P. C.

Annals of Roentgenology, $20.00. (*Paul B. Hoeber, Inc., New York.*) Vol. XIII. *Gynecological Roentgenology.* By JULIUS JARCHO, M.D., F.A.C.S.

Serviceably bound, clearly printed, adequately and well illustrated, this volume brings together a number of interesting studies on the employment of x-ray in obstetrical and gynecological diagnosis and treatment. It should be of real value to gynecologists and to roentgenologists, as well as to all medical students.

There is a short introduction by James T. Case, who has edited the entire system of *Annals of Roentgenology*, of which this is the XIIIth volume.

The author devotes 438 pages to diagnosis, 52 pages to therapy, under which radium, as well as x-ray, is considered. There are 43 pages of bibliography. The subject matter is taken up in 20 chapters. The index is a comprehensive and thorough one.

Owing, perhaps, to the newness of x-ray diagnostic methods and, also, doubtless on account of the appeal to those unfamiliar with gynecological diagnosis and therapy, the author deals with a number of topics in detail which might have been omitted had the book been written solely for gynecologists. Such subjects as the normal anatomy of the pelvic organs, the treatment of sterility, methods of mechanical abortion, the therapeutic value of pneumoperitoneum are interestingly treated but essentially are foreign to the principal subject under treatment.

The author has read and digested an enormous literature and attempts to give priority credit to all of those who have worked with pneumoperitoneal and lipiodol methods of visualizing the pelvis. These methods, which are of undoubted value in determining the patency of the fallopian tubes, have not been generally accepted as routine methods of gynecological diagnosis. Dr. Jarcho feels that there is no danger associated with their use and he quotes from many authorities who have employed them. He excludes malignancy from the conditions to which these procedures are properly applicable. In a separate chapter, he describes in an interesting manner the value of x-ray methods in studying the physiology of peristalsis, and shows how they have added to newer anatomical findings.

While the reader has thoroughly enjoyed going through the text and studying the illustrations, he still is left with a feeling of uncertainty as to whether these methods justify their cost, the discomforts which they entail, and the possible dangers inherent in them in any other conditions than those associated with sterility.

The technic and the instrumentaria, the general indications and contra-indications for using the methods, so far as they have been tested out today, are clearly presented.

The final chapter, dealing with ray therapy, is rather briefly and inadequately elaborated; and one might take exceptions to many of the statements made. This is notable in the treatment of uterine fibroids. There are so many technical methods, and such an immense field for ray treatment in gynecology that this section of the volume is out of proportion to the diagnostic divisions. However, the beginner in gynecological ray therapy will find here many valuable suggestions and a description of apparatus, methods of treatment, and results which should be of real service.

C. F. B.

A Manual of Clinical Laboratory Methods. By CLYDE LOTTRIDGE CUMMER, Ph.B., M.D., F.A.C.P. 3rd Edition, thoroughly revised. Illust. 173 Engravings & 12 plates. 583 Pp. (*Lea & Febiger, Philadelphia, 1931.*)

In reviewing the third edition of Cummer's Manual of Clinical Laboratory Methods, I find it to be a tremendous improvement over the previous editions. It was very gratifying to find that even though additions have been made, the present work is still a compact textbook and laboratory guide with the subject matter in a very concise form, sufficiently to prevent an increase in the number of pages of subject matter, but yet giving enough to make it a very desirable volume for the use of medical students who are apt to be too pressed for time to devote themselves to more than a compact work.

In the present edition, the chapters dealing with bl- unting and pathology of the blood and the anemias have been brought up t has also that dealing with the precipitation tests for syphilis. It is im nd that the volume contained many new methods extracted from th erature, as for example: newer methods of demonstrating oxydase gr e hemoglobin content of the blood, the sedimentation of red blood cells, mpregnation methods for treponemata, the icterus index, tests on spinal flu., etc. The tables of normal findings also prove to be of the greatest importance for quick reference.

As a whole, the present edition of this work should prove to be of the greatest aid to both students and technicians, as it more than satisfactorily answers the requirements.

P. P. S.

Handbook of Anatomy. By JAMES K. YOUNG, M.D., F.A.C.S. Revised by George W. Miller, M.D., F.A.C.S. 7th Revised Edit. 460 Pp. with 154 engravings. (*F. A. Davis Co., Philadelphia, 1930.*)

This compend presents in a simple form the essentials for the study of human anatomy, arranged in tabulated form. As a handy reference book it has long since established its reputation.

G. B.

The Diagnosis & Treatment of Venereal Diseases In General Practice. [The Routine Management of Syphilis and Gonorrhea Employed In The St. Thomas's Hospital Venereal Diseases Department]. By L. W. HARRISON, D.S.O., M.B., F.R.C.P.E. 4th edition. 567 Pp. (*Oxford Univ. Press, London, 1931.*)

This edition is an improvement over its predecessors in that it contains a more detailed description of gonorrhea in women and of soft chancre. The topic of syphilis and its treatment is very completely handled.

P. P. S.

Piersol's Human Anatomy. Including structures and Development and Practical Considerations. 9th edition revised under the supervision of G. Carl Huber. With 1734 illust. of which 1520 are original, and 460 in color. 2104 Pp. (*J. P. Lippincott & Co., Philadelphia, 1930.*)

The ninth edition presents revisions and additions on lymphatics, veins, nervous system and especially the fibrepaths. The B. N. A. nomenclature has been introduced uniformly, a very desirable simplification.

P. P. S.

The Modern Therapeutics of Internal Diseases. By A. P. CAWADIAS. Pp. 147. $3.75. (*William Wood & Co., New York, 1931.*)

We find here a philosophical discussion which presents the author's ideas about the general principles to be followed in outlining a rational plan of treatment for a sick person. He stresses the importance of a complete preliminary examination, but emphasizes the uselessness of elaborate diagnostic studies if no attention be paid to appropriate therapy. The underlying idea of the book is that "there are no *diseases*, but only *diseased individuals*" . . . diseases are fictional constructions made for the purpose of classification of morbid phenomena." Again, "*diseases* can not be treated (since they do not exist); the sick person as a whole must be treated." With reference to the present tendency to narrow-minded specialization, we read: "The only real specialist in internal medicine is the internist—the physician who sees and treats the patient as a whole."

While the style is pompous, and the "going" in places is distinctly "heavy," the author has brought forward some ideas which merit careful consideration by every thoughtful physician. The practitioner seeking practical help on some specific problem should look elsewhere.

P. W. C.

The History of Paediatrics. By GEORGE FREDERIC STILL. Pp. 526. (*Humphrey Milford, Oxford Univ. Press, London, 1931.*)

This is a most interesting and scholarly discourse on the progress of paediatrics from Hippocrates up to the end of the 18th century. It was written by one of England's foremost paediatricians and was originally the basis of his Fitzgerald

Lectures on the History of Medicine, delivered before the College of Physicians of London a few years ago. The author uses the biographical method in presenting the subject but he does not neglect "to trace at the same time the medical interest in children and their diseases." His extracts and reproduction of early paediatric literature are chosen with great care and deliberation. His discussions of priority of description of diseases shows a painstaking analysis of both the man and the subject. Thus, he sweeps aside the personal shortcomings of Daniel Whistler as a possible embezzler of the College funds and pleads for his recognition for the first description of rickets. "It lacks the research in morbid anatomy which was a feature of Glisson's work, but none the less it deserves a more honored place than it has hitherto received as the first published account of an important disease."

His discussion of the life and work of Walter Harris is both amusing and interesting. It portrays the state of medical practice current in that period and the first attempt of rationalism instead of "empyricism" in medicine.

In his preface, Dr. Still humbly apologizes for writing a book much the same as Dr. John Ruhräh's "Pediatrics of the Past." Such apologies are hardly necessary, as the books really supplement one another and differ in many points of view.

The book has an excellent bibliography and an appendix of Inaugural Dissertation bearing on Pediatric subjects. It is well worth reading, even if one does not deal with patients below the age of puberty.

D. H. S.

The Baby's First Two Years. By Richard M. Smith. With illust. New and revised edition. 159 pp. $1.75. (*Houghton Mifflin Co., The Riverside Press, Cambridge.*)

The average busy pediatrician does not have time to give detailed instructions about many things apparently simple to him, yet of paramount importance to the mother, and for this reason this book may be safely recommended. It is the 3rd edition of a booklet published in 1915, and intended for the layman. It consists of 3 sections; the first reviewing the usual rules for the care and feeding of infants, the second containing general suggestions to mothers, and the third presenting briefly a few common recipes and charts. Simply written, almost in conversational tone, the text solves many problems for anxious mothers. The chapter entitled "A Typical Day," which rehearses in diary form the procedure of carrying out step by step the intimate details of any day in the infant's life, is excellent. There is one chapter on habits and training, unfortunately but 6¼ pages in length, which contains much good advice to start the mother off correctly in the early care of her child. A little more emphasis and more detail would enhance the value of this chapter.

S. E. L.